IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF MASSACHUSETTS

MODERNATX, INC. and MODERNA US, INC., Plaintiffs, v. PFIZER INC., BIONTECH SE, BION-TECH MANUFACTURING GMBH, and BIONTECH US INC., Defendants.	C.A. No. _____ **JURY TRIAL DEMANDED**

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs ModernaTX, Inc. and Moderna US, Inc. (collectively, "Moderna" or the "Company"), by and through their attorneys, hereby allege for their patent infringement Complaint against Defendants Pfizer Inc. ("Pfizer"), BioNTech SE, BioNTech Manufacturing GmbH, and BioNTech US Inc. ("BioNTech US," together with BioNTech SE and BioNTech Manufacturing GmbH, "BioNTech") as follows:

NATURE OF THE CASE

A. Moderna Was Founded in 2010 on the Promise of Developing mRNA Technology to Create a New Generation of Transformative Medicines

1. Just twelve years ago, messenger RNA ("mRNA") medicines were a new and unproven technology. Although many doubted that this technology could ever be used to treat or prevent disease, Moderna recognized early on that it had great potential to improve patients' lives. Since Moderna's founding in 2010 in Cambridge, Massachusetts, the Company has been singularly focused on making mRNA medicines a reality through substantial investment and years of research and development.

2. Moderna embodies the American ethos of innovation. Its founders are scientists who challenged the status quo and took a chance on developing this unproven technology to treat and prevent some of the deadliest diseases and medical conditions. They came together to create Moderna, a name created from combining "modified" and "RNA." Throughout its history, Moderna has prioritized science above all else, with a focus on helping patients who do not have other options.

3. Over the past twelve years, Moderna has worked diligently in its laboratories to pioneer several fundamental breakthroughs in the field of mRNA technology. These discoveries span all aspects of mRNA medicines—from the characteristics and design of the mRNA itself and the protein it encodes, to the technologies to deliver mRNA to patients safely and effectively.

4. Built on that research, Moderna is developing medicines that could treat and prevent a wide range of diseases—from infectious diseases like influenza and HIV, to autoimmune and cardiovascular diseases and rare forms of cancer.

5. Part of Moderna's foundational research in this area included advancing the solution to one of the fundamental challenges with mRNA medicines—namely that the body's own immune system can recognize mRNA as a foreign substance and attack it. In 2010, Moderna scientists began studying new chemical modifications to the mRNA that could better avoid provoking an immune response. That work led to the discovery that mRNA molecules with a specific modification in which uridine is replaced with 1-methylpseudouridine were surprisingly superior to other chemically-modified mRNAs. A former top vaccine official at the U.S. Food and Drug

Administration ("FDA") was recently quoted as saying that the chemical change Moderna pioneered is "the most important thing that people have done with mRNA vaccines."[1]

6. Moderna scientists then studied how to deliver that chemically-modified mRNA to cells in the body. In 2011, they tested whether chemically-modified mRNAs could be delivered to cells when formulated in a lipid nanoparticle. These experiments showed for the first time that cells could successfully express the protein encoded by 1-methylpseudouridine modified mRNA when formulated in a lipid nanoparticle. After those successful experiments, Moderna began using 1-methylpseudouridine modified mRNA in a lipid nanoparticle formulation as the foundation of its mRNA platform.

7. In 2014, around the time that a coronavirus that caused "Middle East Respiratory Syndrome" or "MERS" first emerged, Moderna created a division that was focused exclusively on developing mRNA vaccines for infectious disease. In 2015, Company scientists developed an mRNA vaccine for MERS, which encoded for the full-length spike protein of the MERS coronavirus in a lipid nanoparticle. Animal challenge studies showed that the new vaccine successfully resulted in the production of neutralizing antibodies and prevented MERS infection. Those experimental results provided proof of concept that mRNA encoding for the full-length spike protein in a lipid nanoparticle could be used successfully to prevent coronavirus infection.

8. To protect Moderna's substantial investment of time and resources in developing its innovations, Moderna sought and obtained patents protecting the inventions underlying its mRNA platform and disease-specific vaccine designs, including for coronaviruses. These patents were filed between 2011 and 2016.

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[1] Jon Cohen, *New Crop of mRNA Vaccines Aim for Accessibility*, 376 Science 120, 121 (2022), *available at* https://www.science.org/doi/epdf/10.1126/science.abq3935 [https://perma.cc/JBM9-9FLH].

9. As a company that had no commercial products at the time, these patents were among Moderna's most valuable business assets and enabled Moderna, as a startup biotech company, to attract investors who could help the Company fulfill its promise and bring its technologies to patients. Indeed, Pfizer's CEO, Albert Bourla, has stated that patents are crucial to "small biotech innovators that are totally dependent on accessing capital from investors who invest only on the premise that their intellectual property will be protected."[2]

B. Moderna Was Uniquely Prepared to Respond to the COVID-19 Pandemic Based on Its Existing mRNA Platform and Coronavirus Vaccine Work on MERS

10. When the COVID-19 pandemic struck, Moderna had already conducted a decade of foundational research in the area of mRNA medicines, including specifically on coronaviruses, and was uniquely positioned to respond to the crisis.

11. Following Moderna's initial patented discoveries, the Company began partnering in 2017 with scientists at the National Institutes of Health ("NIH") to further develop its MERS vaccine. This experience partnering with the NIH would later prove vital in quickly responding to the COVID-19 pandemic.

12. Moderna was not planning to bring its first product to market—a vaccine for mothers that could prevent birth defects—until the mid-2020s. Prior to COVID-19, almost all of Moderna's employees worked in research and development. But when it became clear that the virus that causes COVID-19 had the potential to create a pandemic, Moderna answered the call. For a company as small as Moderna, with fewer than 1,000 employees at the time, this was no small feat. Nor was it one that came without risk. Moderna diverted resources away from other

[2] Open Letter from Albert Bourla to Pfizer Employees (May 7, 2021), https://www.pfizer.com/news/articles/why_pfizer_opposes_the_trips_intellectual_property_waiver_for_covid_19_vaccines [https://perma.cc/6HSM-QDM5].

projects and hired and built new teams in order to take on the challenge presented by COVID-19. Moderna also issued new stock to raise the funds it would need to manufacture the vaccine. The Company took all of these actions because Moderna had done the research and believed that its mRNA platform could take on this new coronavirus.

13. As a result, in early 2020, Moderna was able to quickly leverage its existing mRNA technology to address the crisis. With its partnership with the U.S. government and in particular the NIH, the Company was able to develop a COVID-19 vaccine that was ready to test in clinical trials within a matter of weeks.

14. While others were predicting that vaccine development could take years, Moderna's COVID-19 vaccine was first administered by the NIH in clinical trials on March 16, 2020, just two months after the genetic sequence for the virus that causes COVID-19 was published. *See, e.g.*, *infra* ¶¶ 48-50.

15. Regulatory authorities set a bar by which to measure COVID-19 vaccines, requiring that they be at least 50% effective in preventing infection. On November 16, 2020, less than a year after COVID had first been identified, Moderna blew away those expectations and was able to show that its vaccine was 94% effective against infection by the strain of the COVID virus then circulating. Other companies using more traditional technology were not able to submit their data until much later and fell short of the bar Moderna had set. Some even abandoned their efforts at a vaccine altogether. Without mRNA vaccines and Moderna's technology, many more months and lives might have been lost.

16. The FDA authorized the use of Moderna's COVID-19 vaccine, which is now marketed under the name Spikevax®, in individuals 18 years of age and older under an emergency

use authorization on December 18, 2020, and the FDA fully approved Spikevax® for use in that population on January 31, 2022.

C. Pfizer and BioNTech Followed the Trail Moderna Blazed for mRNA Vaccines and Copied Moderna's Innovations Without Ever Requesting a License

17. Pfizer and BioNTech also developed an mRNA vaccine for COVID-19, marketed under the brand name Comirnaty®. As explained more fully below, the Pfizer/BioNTech vaccine uses the technology Moderna developed and patented.

18. When COVID-19 emerged, neither Pfizer nor BioNTech had Moderna's level of experience with developing mRNA vaccines for coronaviruses. Upon information and belief, before the emergence of COVID-19, unlike Moderna, neither Pfizer nor BioNTech had ever developed an mRNA vaccine for a coronavirus.

19. Pfizer and BioNTech started with a number of different options when they considered how to design their vaccine. In fact, they took four different candidates into clinical testing, including options that would have steered clear of Moderna's innovative path by using unmodified mRNA. *See, e.g.*, *infra* ¶¶ 73-74. Ultimately, however, Pfizer and BioNTech discarded those alternatives and copied Moderna's patented technology. *See, e.g.*, *infra* ¶¶ 75-76.

20. And they did so knowing that they were following Moderna's lead. Pfizer's CEO, Albert Bourla, acknowledged that the vaccine design Pfizer and BioNTech ultimately chose to pursue uses "the entire spike protein, which . . . Moderna is using." Ex. 4, Transcript of Goldman Sachs Virtual 41st Annual Global Healthcare Conference at 3 (June 9, 2020).

21. Pfizer and BioNTech copied two critical features of Moderna's patented mRNA technology platform. First, out of numerous possible choices, they decided to make the exact same chemical modification to their mRNA that Moderna scientists first developed years earlier, and which the Company patented and uses in Spikevax®. Second, and again despite having many

different options, the Pfizer and BioNTech vaccine encoded for the exact same type of coronavirus protein (i.e., the full-length spike protein), which is the coronavirus vaccine design that Moderna had pioneered based off its earlier work on coronaviruses and which the company patented and uses in Spikevax®. The Moderna inventions that Pfizer and BioNTech chose to copy were foundational for the success of their vaccine.

D. Moderna Is the Only Vaccine Manufacturer to Have Made a Global Commitment to Intellectual Property Never Being a Barrier to COVID-19 Vaccine Access

22. Given the unprecedented challenges of the COVID-19 pandemic, Moderna voluntarily pledged on October 8, 2020 that, "*while the pandemic continues*, Moderna will not enforce our COVID-19 related patents against those making vaccines intended to combat the pandemic."[3] Moderna refrained from asserting its patents earlier so as not to distract from efforts to bring the pandemic to an end as quickly as possible.

23. By early 2022, however, the collective fight against COVID-19 had entered a new endemic phase and vaccine supply was no longer a barrier to access in many parts of the world, including the United States. In view of these developments, Moderna announced on March 7, 2022, that it expected companies such as Pfizer and BioNTech to respect Moderna's intellectual

[3] Press Release, Moderna, Inc., Statement by Moderna on Intellectual Property Matters during the COVID-19 Pandemic (Oct. 8, 2020), https://investors.modernatx.com/Statements--Perspectives/Statements--Perspectives-Details/2020/Statement-by-Moderna-on-Intellectual-Property-Matters-during-the-COVID-19-Pandemic/default.aspx (emphasis added) [https://perma.cc/EMU7-9JAT].

property and would consider a commercially-reasonable license should they request one.[4] This announcement was widely publicized, including through coverage in *The Wall Street Journal*.[5] Critically, however, and to further its belief that intellectual property should never be a barrier to access, as part of this announcement, Moderna committed to never enforce its patents for any COVID-19 vaccine used in the 92 low- and middle-income countries in the Gavi COVAX Advance Market Commitment ("AMC"). This includes any product manufactured outside the AMC-92 countries, such as the World Health Organization's project in South Africa, with respect to COVID-19 vaccines destined for and used in the AMC-92 countries. Although they have continued to use Moderna's intellectual property, Pfizer and BioNTech have not reached out to Moderna to discuss a license.

E. Moderna Brings This Action to Protect the Company's mRNA Technology Platform and Ensure its Innovations Are Respected

24. Despite recognizing the importance of patents to innovators such as Moderna, Pfizer and BioNTech have copied Moderna's intellectual property and have continued to use Moderna's inventions without permission.

25. Moderna therefore brings this lawsuit to protect the mRNA technology platform it innovated, invested in, and patented and to ensure that intellectual property is respected.

26. In non-AMC 92 countries, where vaccine supply is no longer a barrier to access, Moderna expects Pfizer and BioNTech to stop infringing the Company's intellectual property. Compensating Moderna with monetary damages for using its patented technology will enable the

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[4] Press Release, Moderna, Inc., Moderna's Updated Patent Pledge (Mar. 7. 2022), https://investors.modernatx.com/Statements--Perspectives/Statements--Perspectives-Details/2022/Modernas-Updated-Patent-Pledge/default.aspx [https://perma.cc/R7KP-74FJ].

[5] *See* Peter Loftus, *Moderna Signals It May Enforce Covid-19 Vaccine Patents in Wealthy Nations*, Wall Street J., (Mar. 7, 2022, 7:33 PM), https://www.wsj.com/articles/moderna-signals-it-may-enforce-covid-19-vaccine-patents-in-wealthy-nations-11646699609 [https://perma.cc/CC7N-2JPS].

Company to continue investing in its mRNA technology platform so that it can develop medicines that can treat and prevent a wide range of diseases.

27. This lawsuit is based on three patents that claim priority to applications filed between 2011 and 2016 covering Moderna's foundational intellectual property, and the Company is seeking damages for revenue Pfizer and BioNTech derived from sales in the United States that are not subject to 28 U.S.C. § 1498 and from its domestic manufacture for supply to non-AMC 92 countries outside the United States.

28. This lawsuit does not relate to any patent rights generated during Moderna and NIH's collaboration to combat COVID-19. In addition, in recognition of the need for ensuring access to these critical vaccines, this lawsuit is narrowly drawn in terms of the relief it seeks. Moderna is not seeking an injunction: it is not seeking to remove Comirnaty® from the market or to prevent its future sale. Consistent with Moderna's patent pledge, Moderna is not seeking damages for activities occurring before March 8, 2022. And Moderna is not seeking damages related to Pfizer and BioNTech's sales to the 92 low- and middle-income countries in the Gavi COVAX Advance Market Commitment.

PARTIES

29. ModernaTX, Inc. ("ModernaTX") is a corporation organized and existing under the laws of Delaware, having its principal place of business at 200 Technology Square, Suite 300, Cambridge, MA 02139. ModernaTX is a wholly-owned subsidiary of Moderna, Inc. ModernaTX is the owner by assignment of the patents asserted in this litigation.

30. Moderna US, Inc. ("Moderna US") is a corporation organized and existing under the laws of Delaware, having its principal place of business at 200 Technology Square, Suite 300, Cambridge, MA 02139. Moderna US is a wholly-owned subsidiary of Moderna, Inc. Moderna

US is the exclusive licensee of the patents asserted in this litigation, and Moderna US sells Spikevax® in the United States.

31. Moderna is a pioneer in the field of mRNA medicines. Since its founding in 2010, Moderna has through years of research and development created the most advanced platform for mRNA medicines in the world. In addition to Spikevax®, Moderna has a pipeline of several dozen mRNA vaccines and therapeutic medicines for a wide range of diseases.

32. Upon information and belief, Pfizer is a corporation organized and existing under the laws of Delaware, with its principal place of business at 235 East 42nd Street, New York, NY 10017. Pfizer has regular and established places of business at 1 Portland Street, Cambridge, MA 02139 and 1 Burtt Road, Andover, MA 01810.

33. Upon information and belief, BioNTech SE is a corporation organized and existing under the laws of Germany, with its principal place of business at An der Goldgrube 12, Mainz, 55131 Germany.

34. Upon information and belief, BioNTech Manufacturing GmbH, a wholly-owned subsidiary of BioNTech SE, is a limited liability company organized and existing under the laws of Germany, with its principal place of business at An der Goldgrube 12, Mainz, 55131 Germany. BioNTech Manufacturing GmbH is the Biologics License Application ("BLA") holder for Comirnaty® in the United States.

35. Upon information and belief, BioNTech US, a wholly-owned subsidiary of BioNTech SE, is a corporation organized and existing under the laws of Delaware, with its principal place of business at 40 Erie St., Suite 110, Cambridge, MA 02139. BioNTech US's office in

Cambridge, MA serves as BioNTech's North American headquarters.[6] BioNTech US is BioNTech's agent for service of process in the United States.[7]

36. Upon information and belief, Pfizer and BioNTech together developed and commercialize Comirnaty®.

JURISDICTION AND VENUE

37. This is an action for patent infringement arising under the patent laws of the United States, 35 U.S.C. § 1, et. seq. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

38. This Court has personal jurisdiction over Defendants because of their systematic and continuous contacts with Massachusetts. For example, both Pfizer and BioNTech regularly conduct business within Massachusetts, including at Pfizer's facilities located at 1 Portland Street, Cambridge, MA 02139 and 1 Burtt Road, Andover, MA 01810, and at BioNTech's facility located at 40 Erie St, Suite 110, Cambridge, MA 02139, which serves as BioNTech US's North American headquarters. Both Pfizer and BioNTech have specifically directed their business activities making and selling Comirnaty® to Massachusetts, including by manufacturing the mRNA drug substance for Comirnaty® at Pfizer's facility in Andover, Massachusetts. Defendants' actions that give rise to personal jurisdiction further include, but are not limited to: making, using, selling, and offering for sale Comirnaty® in Massachusetts; knowing and intending that Comirnaty® would be used in Massachusetts; deriving substantial revenue from the use of Comirnaty® in Massachusetts; and expecting their infringing actions to have consequences in Massachusetts.

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[6] *See, e.g.*, BioNTech SE, Annual Report (Form 20-F) 179, F-12 (Mar. 30, 2021), *available at* https://investors.biontech.de/static-files/e862a8ea-5d90-4672-acfb-34de57b58806.

[7] *See, e.g.*, BioNTech SE, Annual Report (Form 20-F) 81 (Mar. 30, 2022), *available at* https://investors.biontech.de/static-files/50d0cafc-b2c1-4392-a495-d252f84be105.

39. Pfizer and BioNTech have also purposefully availed themselves of the benefits and protections of the courts in Massachusetts, including by initiating litigation relating to Comirnaty® before this Court. *See BioNTech SE v. CureVac AG*, C.A. No. 22-11202 (D. Mass.) (filed July 25, 2022).

40. Venue is proper as to BioNTech SE and BioNTech Manufacturing GmbH in this District pursuant to, inter alia, 28 U.S.C. § 1391(c)(3).

41. Venue also is proper as to all Defendants in this District under 28 U.S.C. § 1400(b). Both Pfizer and BioNTech have regular and established places of business in this District, including Pfizer's facilities located at 1 Portland Street, Cambridge, MA 02139 and 1 Burtt Road, Andover, MA 01810, and at BioNTech's facility located at 40 Erie St, Suite 110, Cambridge, MA 02139, which serves as the North American headquarters for BioNTech. Defendants have committed acts of infringement and, upon information and belief, will commit further acts of infringement in Massachusetts.

MODERNA'S PIONEERING WORK ON mRNA MEDICINES

42. Long before COVID-19 first emerged, Moderna recognized that mRNA had the potential to revolutionize the field of medicine. mRNA is a molecule that instructs cells to make particular proteins. Unlike traditional vaccines and therapeutics, mRNA medicines harness the body's own cellular machinery to make proteins themselves that can treat or prevent disease. mRNA medicines use a specific nucleotide sequence to encode instructions to make the exact protein needed for a particular disease. This makes mRNA medicines a powerful tool that can be programmed to target specific diseases. However, before Moderna began its research, nobody had figured out how to make or use mRNA medicines successfully. Moderna was founded in 2010 with the sole focus on solving those challenges to make mRNA medicines a reality for patients.

43. Along the way, Moderna encountered many technical challenges as it attempted to develop an entirely new way to treat and prevent disease. The problems that Moderna faced started with the mRNA itself. mRNA is an unstable molecule that is quickly destroyed inside the body. Moderna scientists had to develop novel ways to stabilize mRNA by modifying its chemical structure so that it could be used in vaccines and therapeutics. Moderna also optimized its mRNA platform to make it more effective at producing the proteins needed to fight and prevent disease. And Moderna developed new techniques for manufacturing mRNA medicines so that they could be made on a large scale. All told, Moderna invested billions of dollars over the course of nearly a decade of research to develop an mRNA platform that could be applied across a variety of therapeutic and prophylactic applications.

44. Moderna was also at the forefront of applying its mRNA medicines to new diseases as they emerged. For example, Moderna had previously developed an mRNA vaccine against a coronavirus that caused Middle Eastern Respiratory Syndrome, or "MERS." Through that work on MERS, Moderna demonstrated the effectiveness of mRNA vaccines to prevent coronavirus infection and developed a template that could be used for vaccines against future coronaviruses.

MODERNA'S COVID-19 VACCINE

45. When COVID-19 first emerged, nobody was better positioned to respond than Moderna. Moderna had already developed the world's most advanced platform for mRNA medicines. And Moderna had experience developing mRNA vaccines to prior coronaviruses through its research on MERS.

46. Unlike Pfizer and BioNTech, Moderna did not struggle with different approaches before designing its COVID-19 vaccine. Instead, working from its research completed years earlier, Moderna knew how to design an effective COVID-19 vaccine and was able to respond rapidly

with a vaccine specifically targeting COVID-19 in early 2020 when reports of COVID-19 first began to emerge from China.

47. Moderna partnered with leading scientists from the NIH to test and develop Moderna's COVID-19 vaccine. The NIH had access to laboratories to conduct pre-clinical testing of Moderna's COVID-19 vaccine, including through challenge studies demonstrating the ability of Moderna's new vaccine to prevent COVID-19 infection. Moderna and the NIH also met regularly to develop a clinical trial strategy to evaluate the safety and efficacy of Moderna's COVID-19 vaccine.

48. The genomic sequence for SARS-CoV-2 was first published on January 11, 2020, and, within a matter of days, Moderna took that information to create an mRNA sequence encoding for the virus's spike protein. The first clinical batch of Moderna's COVID-19 vaccine was manufactured on February 7, 2020—just four weeks after the genome sequence for SARS-CoV-2 was published. Moderna provided clinical samples to its partners at the NIH. Moderna and the NIH then worked together to conduct clinical trials of Moderna's vaccine on an expedited basis.

49. Moderna's new mRNA technology dramatically changed the pace of vaccine development. While other leading pharmaceutical companies thought that it could take "several years" or more before a vaccine would be ready, Moderna's CEO, Stéphane Bancel, predicted in March 2020 that Moderna could have its vaccine in Phase II and III clinical trials in just a "few months."[8]

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[8] *See* Remarks by President Trump and Members of the Coronavirus Task Force in Meeting with Pharmaceutical Companies (Mar. 2, 2020), https://trumpwhitehouse.archives.gov/briefings-statements/remarks-president-trump-members-coronavirus-task-force-meeting-pharmaceutical-companies/ [https://web.archive.org/web/20200303160403/https://www.whitehouse.gov/briefingsstatements/remarks-president-trump-members-coronavirus-task-force-meeting-pharmaceutical-companies/].

50. He was right. Spikevax® has had a significant effect in preventing infections, transmission, hospitalizations, and deaths resulting from COVID-19. Spikevax® was approved for clinical trials on March 4, 2020 and became the first COVID-19 vaccine candidate to enter Phase I clinical trials in humans in the United States. On March 16, 2020, the first participant in the Phase I study of Spikevax® was dosed, with a Phase II trial beginning in May 2020 and a Phase III trial in July 2020. Those clinical trials showed that Spikevax® was 94% effective at preventing a COVID-19 infection from the original coronavirus strain after completing a two-dose regimen, and it remained 93% effective six months after administration.

51. The FDA authorized the use of Spikevax® in individuals 18 years of age and older under an emergency use authorization on December 18, 2020, and the FDA fully approved Spikevax® for use in that population on January 31, 2022.

52. On October 20, 2021, the FDA expanded its emergency use authorization for Moderna's COVID-19 vaccine to permit the administration of a booster dose in certain individuals who previously completed their primary two-dose regimen with Moderna's COVID-19 vaccine. On November 19, 2021, the FDA amended its emergency use authorization to permit individuals to receive a booster dose of Moderna's COVID-19 vaccine six months after completion of their primary dosing regimen with any FDA-authorized or approved COVID-19 vaccine. After the Omicron variant of COVID-19 emerged, the FDA on January 7, 2022 shortened the dosing interval for a booster dose of Moderna's COVID-19 vaccine to five months after the completion of the individual's primary vaccination series. On March 29, 2022, the FDA expanded Moderna's emergency use authorization to permit the administration of a second booster dose to individuals 50 years of age and older and to immunocompromised individuals 18 years of age and older. On June

17, 2022, the FDA expanded Moderna's emergency use authorization to permit the use of Moderna's COVID-19 vaccine in children six months and older.

53. Moderna has supplied the United States with over 299 million doses of Moderna's COVID-19 vaccine, and over 77 million people in the United States have received a complete primary vaccine series with Moderna's COVID-19 vaccine to date.

MODERNA'S PATENTS

54. The success of Spikevax® is a result of the groundbreaking innovations that Moderna made in the years before COVID-19 first emerged. Moderna has sought to protect its substantial investment in research and development by obtaining patents that cover its inventions. Three of those patents are at issue here: U.S. Patent Nos. 10,898,574 (the "'574 patent"), 10,702,600 (the "'600 patent"), and 10,933,127 (the "'127 patent") (collectively, the "Asserted Patents").

A. Moderna's mRNA Platform Technology

55. mRNA is a molecule that typically is composed of four different nucleosides: adenosine, guanosine, cytidine, and uridine. The nucleoside sequence in an mRNA molecule provides instructions that cells use to create particular proteins.

56. One of the early challenges that Moderna faced in developing mRNA medicines was that administering them to people can result in the body's own immune system attacking the mRNA molecule. This immune response destroys the mRNA before it can have its intended effect. To solve that problem, Moderna studied numerous different potential chemical modifications to the mRNA molecule itself to disguise the mRNA from the body's immune system. By substituting one of the typical nucleosides in mRNA with a chemically-modified version, Moderna hoped that it could prevent the body's immune system from recognizing and destroying the mRNA molecule.

While certain chemical modifications had been tested before, Moderna set out to improve upon that work to identify the best chemical modifications to use in an mRNA vaccine.

57. Moderna's scientists made the groundbreaking discovery that replacing uridine in the mRNA molecule with 1-methylpseudouridine resulted in surprisingly superior protein production—a severalfold increase over chemically-modified mRNAs studied before—with a significantly reduced immune response against the mRNA itself. Moderna further discovered that packaging that chemically-modified mRNA in a lipid nanoparticle formulation allowed for the efficient delivery of the mRNA to cells.

58. This work became the foundation of Moderna's mRNA platform. Moderna's '574 patent describes and claims the results of that research. Moderna's early discovery captured in the '574 patent has been critical to the success of mRNA vaccines for COVID-19. Although Pfizer and BioNTech initially considered alternative vaccine designs without a chemical modification, they ultimately chose to use one, and not just any one. They chose to use the very same 1-methylpseudouridine modification first pioneered by Moderna years earlier.

59. The '574 patent is titled "Delivery and formulation of engineered nucleic acids." The '574 patent names Moderna scientists Antonin de Fougerolles and Sayda M. Elbashir as inventors. The '574 patent claims priority to a provisional patent application filed on March 31, 2011 and a non-provisional patent application filed on April 2, 2012. The '574 patent issued on January 26, 2021, and is assigned to Moderna. A true and correct copy of the '574 patent is attached as Exhibit 1.

60. The ’574 patent claims Moderna’s mRNA platform technology, which utilizes mRNA encoding for a polypeptide that comprises a modified uracil, including 1-methylpseudouridine, in a lipid nanoparticle formulation. The ’574 patent claims both methods of producing a polypeptide of interest and pharmaceutical compositions.

61. Moderna practices the ’574 patent through its Spikevax® vaccine, and Moderna marks Spikevax® with a reference to its patent marking website (https://www.modernatx.com/patents [https://perma.cc/B6AG-6URD]), which identifies the ’574 patent for Spikevax®.

B. Coronavirus Vaccines

62. Before COVID-19 first emerged, Moderna made significant breakthroughs in the development of coronavirus vaccines. Coronaviruses are a class of viruses that are enveloped in a protein shell that is covered on the surface by a “spike” protein. A coronavirus spike protein allows the virus to attach to and infect host cells.

63. When another coronavirus, MERS, first emerged in the mid-2010s, Moderna carefully studied, designed and tested a vaccine for MERS. The MERS vaccine that Moderna developed was based on mRNA encoding for the virus’s spike protein. However, coronavirus spike proteins are large molecules, and no one had previously developed an mRNA vaccine targeting an antigen protein of that size before.

64. Moderna was the first to discover that using mRNA encoding for a full-length coronavirus spike protein in a lipid nanoparticle formulation was highly effective at producing neutralizing antibodies to the coronavirus. Moderna’s research showed that its coronavirus vaccine produced neutralizing antibodies that prevented infection and confirmed that targeting the spike protein was a successful vaccine design that could be applied to other coronaviruses. Moderna’s ’600 and ’127 patents describe and claim the results of that research.

65. When COVID-19 first emerged, this prior research allowed Moderna to design a vaccine for SARS-CoV-2 in record time. Moderna used the coronavirus vaccine design described and claimed in the '600 and '127 patents to develop an mRNA vaccine for COVID-19 by using mRNA encoding for the full-length spike protein for SARS-CoV-2 in a lipid nanoparticle formulation. Although Pfizer and BioNTech initially considered alternative vaccine designs, they ultimately chose to follow Moderna's path of using mRNA encoding for the full-length spike protein of SARS-CoV-2—the exact same design used in Moderna's Spikevax®.

66. The '600 patent is titled "Betacoronavirus mRNA vaccine." The '600 patent names as inventors Moderna scientists Giuseppe Ciaramella and Sunny Himansu. The '600 patent claims priority to provisional patent applications filed in October 2015 and a PCT application filed on October 21, 2016. The '600 patent issued on July 7, 2020, and is assigned to Moderna. A true and correct copy of the '600 patent is attached as Exhibit 2.

67. The '600 patent claims compositions comprising mRNA comprising an open reading frame encoding a betacoronavirus S protein or S protein subunit formulated in a lipid nanoparticle.

68. Moderna practices the '600 patent through its Spikevax® vaccine, and Moderna marks Spikevax® with a reference to its patent marking website (https://www.modernatx.com/patents [https://perma.cc/B6AG-6URD]), which identifies the '600 patent for Spikevax®.

69. The '127 patent is titled "Betacoronavirus mRNA vaccine." The '127 patent names as inventors Moderna scientists Giuseppe Ciaramella and Sunny Himansu. The '127 patent claims priority to provisional patent applications filed in October 2015 and a PCT application filed on October 21, 2016. The '127 patent issued on March 2, 2021, and is assigned to Moderna. A true and correct copy of the '127 patent is attached as Exhibit 3.

70. The '127 patent claims methods of administering to a subject mRNA comprising an open reading frame encoding a betacoronavirus S protein or S protein subunit formulated in a lipid nanoparticle to induce in the subject an immune response to the S protein or S protein subunit, wherein the lipid nanoparticle comprises certain specified percentages of ionizable cationic lipid, neutral lipid, cholesterol, and PEG-modified lipid.

71. The administration of Moderna's Spikevax® in accordance with its approved package insert practices the methods claimed in the '127 patent.

PFIZER AND BIONTECH'S COVID-19 VACCINE

72. Prior to the emergence of COVID-19, Pfizer and BioNTech had begun researching an mRNA vaccine for influenza, but lacked Moderna's expertise in developing mRNA vaccines for coronaviruses and other infectious diseases. Indeed, BioNTech's CEO, Uğur Şahin, had stated that infectious disease targets were "not a priority" for his company before COVID-19.[9] Upon information and belief, Pfizer lacked any candidates in clinical trials using mRNA technology before COVID-19, and BioNTech did not have any such candidates in clinical trials for infectious diseases.[10] By contrast, Moderna had six mRNA candidates for infectious diseases in clinical trials by the time COVID-19 arrived.

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[9] Asher Mullard, *COVID-19 Vaccine Success Enables a Bolder Vision for mRNA Cancer Vaccines, Says BioNTech CEO*, 20 Nature Revs.: Drug Discovery 500 (June 17, 2021), *available at* https://www.nature.com/articles/d41573-021-00110-x ("[Q.] Prior to the pandemic, your first priority was cancer therapies. How much will you now focus on infectious disease vaccines? [A.] We were always interested in infectious diseases, but they were not a priority.") [https://perma.cc/GV6C-UD74].

[10] BioNTech, *Fourth Quarter and Full Year 2019 Corporate Update and Financial Results* 10-11 (Mar. 31, 2020), https://investors.biontech.de/static-files/a718a9ec-53cd-42b6-a6e0-8dd21ca4d907.

73. Although Pfizer and BioNTech initially started their development of an mRNA vaccine for COVID-19 behind Moderna technologically, they quickly made up ground by co-opting Moderna's patented inventions. Pfizer and BioNTech had many choices for how they could design their COVID-19 vaccine. Indeed, upon information and belief, Pfizer and BioNTech's COVID-19 vaccine program—named "Project Lightspeed"—started with more than twenty vaccine candidates representing different mRNA constructs and target antigens that BioNTech took into preclinical testing. By April 23, 2020, Pfizer and BioNTech had narrowed that field down to four vaccine candidates that they chose to take into clinical testing.[11]

74. Not all of Pfizer and BioNTech's COVID-19 vaccine candidates used Moderna's patented inventions. For example, upon information and belief, Pfizer and BioNTech investigated a vaccine candidate called "BNT162a1," which used mRNA containing unmodified uridine. Pfizer and BioNTech also studied a vaccine candidate called "BNT162c2," which used a self-amplifying mRNA technology.[12] Neither BNT162a1 nor BNT162c2 use Moderna's patented mRNA platform containing 1-methylpsuedouridine modified mRNA in a lipid nanoparticle formulation.

75. However, as Pfizer and BioNTech got further along in their clinical development, they ultimately focused exclusively on vaccine designs that used Moderna's patented technologies.

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[11] BioNTech, *BNT162 COVID-19 Vaccine Program Update* 6, 13 (Apr. 23, 2020), https://investors.biontech.de/static-files/398d9bd8-e2cb-49ca-9d6d-7dfd01c66b8a.

[12] Pfizer, *COVID-19 Vaccine Development Program* 6 (July 1, 2020), https://s28.q4cdn.com/781576035/files/doc_presentation/2020/07/01/COVID-Vaccine-Analyst-Call-Deck-v15-presentation.pdf [https://perma.cc/B269-RQ2K]; Pfizer, *Pfizer Inc to Discuss Data From an Ongoing Phase 1/2 Study of mRNA-Based Vaccine Candidate Against SARS-CoV-2 Call* 3 (July 1, 2020), https://s28.q4cdn.com/781576035/files/doc_downloads/event-announcement/2020/07/01/PFE-USQ_Transcript_2020-07-01.pdf [https://perma.cc/5BS7-GY45]; BioNTech, *Second Quarter 2020 Corporate Update and Financial Results* 19 (Aug. 11, 2020), https://investors.biontech.de/static-files/ed9d3efd-2dfb-4f48-955a-69718604d604.

In doing so, Pfizer and BioNTech were aware of Moderna's COVID-19 vaccine design, and they chose to copy it. *See* Ex. 4 at 3 (Pfizer's CEO, Albert Bourla, stating: "We are using an mRNA, modified RNA technology. . . . [O]ne antigen that we're using it [sic] is the entire spike protein, which . . . Moderna is using."); Ex. 5, Transcript of RBC Capital Markets Global Healthcare Conference at 5 (May 19, 2020) (Pfizer's Vice President of Investor Relations, Chuck Triano, stating: "[W]e're testing, not just the spike protein . . . that's Moderna's approach, but in addition, we're testing both the spike and the receptor binding domain."); Ex. 6, Transcript of BioNTech Q2 2020 Earnings Call at 22 (Aug. 11, 2020) (BioNTech's CEO, Uğur Şahin, stating: "[The] modified messenger RNA platform . . . used for the candidate[s] b1 and b2 . . . w[as] selected based on the experience of the field in the past with MERS and [] SARS[.]").

76. On July 27, 2020, Pfizer and BioNTech announced they had chosen to advance a single COVID-19 vaccine candidate called "BNT162b2" to Phase II/III clinical trial.[13] BNT162b2 uses the exact same 1-methylpseudouridine chemical modification in a lipid nanoparticle formulation as Moderna's patented COVID-19 vaccine. Moreover, BNT162b2 contains mRNA encoding for the exact same full-length spike protein for SARS-CoV-2 as Moderna's patented COVID-19 vaccine.

77. Pfizer and BioNTech's strategy of copying Moderna's COVID-19 vaccine design has proven highly successful. On November 18, 2020, Pfizer and BioNTech announced that BNT162b2 showed 95% efficacy against the original coronavirus strain in study participants who

[13] Pfizer Inc., Press Release, Pfizer and BioNTech Choose Lead mRNA Vaccine Candidate Against COVID-19 and Commence Pivotal Phase 2/3 Global Study (July 27, 2020), https://biontechse.gcs-web.com/news-releases/news-release-details/pfizer-and-biontech-choose-lead-mrna-vaccine-candidate-against [https://web.archive.org/web/20200730054155/https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-choose-lead-mrna-vaccine-candidate-0].

had no prior SARS-CoV-2 infection. On December 11, 2020, the FDA granted emergency use authorization for the use of BNT162b2 in individuals over 16 years of age. On August 23, 2021, the FDA approved the BLA for Comirnaty® (BNT162b2) for use in individuals over 16 years of age. Upon information and belief, BioNTech Manufacturing GmbH is the BLA holder for Comirnaty®.

78. On October 29, 2021, the FDA authorized the use of Pfizer and BioNTech's COVID-19 vaccine in children between 5 and 11 years of age pursuant to an emergency use authorization. On June 17, 2022, the emergency use authorization for Pfizer and BioNTech's vaccine was expanded to include the use of the vaccine in individuals between six months and 4 years of age.

79. On September 22, 2021, the FDA amended its emergency use authorization for Comirnaty® to permit administration of a booster dose in certain individuals six months after completing their primary two-dose series with Comirnaty®. On November 19, 2021, the FDA expanded its emergency use authorization to permit a booster dose of Comirnaty® for individuals who are at least 18 years old and allowed for the administration of a Comirnaty® booster in individuals who completed their primary vaccination series with any FDA-authorized or approved COVID-19 vaccine. The FDA further expanded its emergency use authorization to permit a booster dose of Comirnaty® in 16- and 17-year-olds on December 9, 2021 and for individuals 12-years-old or older on January 3, 2022. On January 3, 2022, the FDA also shortened the time period for administration of the third booster dose of Comirnaty® to five months after competition of the primary vaccination series. On March 29, 2022, the FDA authorized individuals who are over the age of 50 or immunocompromised patients who are 12-years-old or older to receive a second booster dose of Comirnaty® four months after receiving a first booster dose. Pfizer and BioNTech

encourage the administration of booster doses of Comirnaty® in accordance with its emergency use authorization, including through the website for their COVID-19 vaccine: https://www.comirnaty.com/booster-dose/ [https://perma.cc/7WHG-LZ3B].

80. Pfizer and BioNTech have enjoyed a substantial financial windfall from their use of Moderna's patented technologies. To date, Pfizer and BioNTech have provided over 472 million doses of their COVID-19 vaccine for use in the United States. Pfizer reported that it earned $7.8 billion in revenues from the sale of Comirnaty® in the United States in 2021, and Pfizer recently announced that it expects an additional $32 billion in global revenues from Comirnaty® in 2022. *See* Rachel Arthur, *Pfizer Predicts $54bn in 2022 Revenue from Comirnaty and Paxlovid*, BioPharma-Reporter.com (Feb. 8, 2022, 15:45 GMT), https://www.biopharma-reporter.com/Article/2022/02/08/Pfizer-predicts-54bn-in-2022-sales-from-Comirnaty-and-Paxlovid [https://perma.cc/9T43-3JHT]; *see also* Press Release, Pfizer, Pfizer Reports Fourth-Quarter and Full-Year 2021 Results 35 (Feb. 8, 2022), https://s28.q4cdn.com/781576035/files/doc_financials/2021/q4/Q4-2021-PFE-Earnings-Release.pdf [https://perma.cc/LLJ4-566V].

81. Moderna is not seeking any relief in this lawsuit for sales that Pfizer and BioNTech have made to the U.S. government that are covered by 28 U.S.C. § 1498. But Pfizer and BioNTech have made clear that they intend to continue to reap profits from their use of Moderna's patented technology in 2022 and beyond, including by making product in the United States to serve the global market. For example, in December 2021, the Committee for Medicinal Products for Human Use of the European Medicines Agency approved Pfizer and BioNTech's request to scale up pro-

duction at Pfizer's facility in Andover, Massachusetts "to support the continued supply of Comirnaty in the European Union."[14] Pfizer and BioNTech have also made clear that they intend to sell additional booster doses of Comirnaty®. For example, on March 29, 2022, the FDA authorized certain people to receive a second booster dose of Pfizer and BioNTech's COVID-19 vaccine.[15] Pfizer and BioNTech actively promote the use of booster doses for their COVID-19 vaccine, including through their website for Comirnaty®: https://www.comirnaty.com/booster-dose/ [https://perma.cc/7WHG-LZ3B].

82. In the face of that ongoing infringement, Moderna filed this lawsuit so that it may obtain fair compensation for Pfizer and BioNTech's continued use of Moderna's patented technologies. That fair compensation will translate into an opportunity for Moderna to reinvest in its leading mRNA platform that allowed both Moderna and Pfizer/BioNTech to address the COVID-19 pandemic. Indeed, were Pfizer and BioNTech allowed to freely copy Moderna's patented technology for their own benefit, the next generation of biotech startups would lose their ability to rely on the patent system that is the bedrock upon which future medicines will be discovered.

COUNT I – INFRINGEMENT OF THE '574 PATENT

83. Moderna incorporates each of the above paragraphs 1-82 as though fully set forth herein.

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[14] European Medicines Agency, *Increase in Manufacturing Capacity for COVID-19 Vaccines from Janssen, Moderna, and BioNTech/Pfizer* (Dec. 16, 2021), https://www.ema.europa.eu/en/news/increase-manufacturing-capacity-covid-19-vaccines-janssen-moderna-biontech-pfizer [https://perma.cc/43DL-YXK9].

[15] Pfizer, Inc., Press Release, Pfizer and BioNTech Receive Expanded U.S. Emergency Use Authorization for an Additional COVID-19 Vaccine Booster in Individuals Aged 50 Years and Older (Mar. 29, 2022), https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-receive-expanded-us-emergency-use [https://perma.cc/BRL9-NX8P].

84. Upon information and belief, Defendants have directly infringed and continue to directly infringe one or more of the claims of the '574 patent, either literally or under the doctrine of equivalents, by making, using, selling, offering for sale, and/or importing Comirnaty® in the United States and in this District without authority, in violation of 35 U.S.C. § 271(a).

85. Upon information and belief, the use of Comirnaty® in accordance with its approved package insert and/or emergency use authorization infringes one or more of the claims of the '574 patent. Defendants have induced infringement and continue to induce infringement of one or more of the claims of the '574 patent, either literally or under the doctrine of equivalents, by encouraging others, including but not limited to healthcare providers and patients, to make and use Comirnaty® in the United States and in this District in a manner that would directly infringe the '574 patent. Defendants have intentionally encouraged and will continue to intentionally encourage acts of direct infringement by others, including but not limited to healthcare providers and patients, with knowledge of the '574 patent and with knowledge that their acts are encouraging infringement, in violation of 35 U.S.C. § 271(b).

86. Upon information and belief, Comirnaty® constitutes a material part of the invention of one or more claims of the '574 patent and is not a staple article or commodity of commerce suitable for substantial noninfringing use. Defendants have contributorily infringed and continue to contributorily infringe one or more of the claims of the '574 patent, either literally or under the doctrine of equivalents, by promoting the making and use of Comirnaty® in accordance with its approved package insert and/or emergency use authorization in the United States and in this District by others, including but not limited to healthcare providers and patients, and knowing that Comirnaty® is especially made or especially adapted for use to infringe the '574 patent, in violation of 35 U.S.C. § 271(c).

87. Upon information and belief, Defendants have infringed or will infringe one or more of the claims of the '574 patent, either literally or under the doctrine of equivalents, in violation of 35 U.S.C. § 271(f), including by supplying the global market for Comirnaty® with components, such as mRNA, manufactured in the United States.

88. Comirnaty® satisfies each and every element of one or more claims of the '574 patent. Defendants' actions with respect to Comirnaty® have infringed, induced infringement, or contributorily infringed at least claims 1-4 and 6-10 of the '574 patent.

89. For example, claim 2 of the '574 patent is representative and recites:

> A pharmaceutical composition comprising:
>
> > a plurality of lipid nanoparticles comprising a cationic lipid, a sterol, and a PEG-lipid,
> >
> > wherein the lipid nanoparticles comprise an mRNA encoding a polypeptide,
> >
> > wherein the mRNA comprises one or more uridines, one or more cytidines, one or more adenosines, and one or more guanosines and wherein substantially all uridines are modified uridines.

90. Comirnaty® is a pharmaceutical composition comprising a plurality of lipid nanoparticles comprising a cationic lipid, a sterol, and a PEG-lipid, wherein the lipid nanoparticles comprise an mRNA encoding a polypeptide, wherein the mRNA comprises one or more uridines, one or more cytidines, one or more adenosines, and one or more guanosines and wherein substantially all uridines are modified uridines.

91. For example, Section 12 of the package insert for Comirnaty® states that "[t]he nucleoside-modified mRNA in COMIRNATY is formulated in lipid particles, which enable delivery of the mRNA into host cells to allow expression of the SARS-CoV-2 S antigen." Section 11 of the package insert for Comirnaty® states that "[e]ach 0.3 mL dose of the COMIRNATY . . .

also includes the following ingredients: lipids (0.43 mg ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2-(polyethylene glycol 2000)-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose." Section 11 of the package insert for Comirnaty® further states that "[e]ach 0.3 mL dose of COMIRNATY . . . contains 30 mcg of a nucleoside-modified messenger RNA (mRNA) encoding the viral spike (S) glycoprotein." A true and correct copy of the package insert from July 2022 for Comirnaty® is attached as Exhibit 7.

92. Defendants' own publications confirm that the uridines in Comirnaty® are modified uridines—namely, 1-methylpseudouridine. For example, Defendants published an article in the journal Nature, which describes making Comirnaty® (BNT162b2) using 1-methylpseudouridine instead of uridine: "Here we report the preclinical development of lipid-nanoparticle-formulated, N^1-methyl-pseudouridine (m1Ψ) nucleoside-modified mRNA (modRNA) BNT162b vaccine candidates (BNT162b1 and BNT162b2) that encode immunogens derived from the S of SARS-CoV-2." Annette B. Vogel et al., *BNT162b Vaccines Protect Rhesus Macaques from SARS-CoV-2*, 592 Nature 283, 284 (2021). A true and correct copy of this publication is attached as Exhibit 8.

93. Claim 9 of the '574 patent recites:

> The pharmaceutical composition of claim 2, wherein the modified uridine is 1-methyl-pseudouridine.

94. Comirnaty® satisfies all of the limitations of claim 9 of the '574 patent for all of the reasons described in paragraphs 90-92 above.

95. Defendants promote the use of Comirnaty® to infringe one or more claims of the '574 patent. For example, Sections 1 and 2 of the package insert for Comirnaty® instruct how to use the vaccine.

96. Defendants further promote the use of Comirnaty® booster shots to infringe one or more claims of the '574 patent. For example, among other things, Pfizer and BioNTech maintain a website (https://www.comirnaty.com/booster-dose/ [https://perma.cc/7WHG-LZ3B]) that promotes the use of Comirnaty® booster shots in accordance with the FDA's emergency use authorization. Pfizer and BioNTech also provide a "Fact Sheet" that instructs the use of Comirnaty® booster shots to infringe one or more claims of the '574 patent. *See* Ex. 9, Vaccine Information Fact Sheet for Recipients and Caregivers about Comirnaty (COVID-19 Vaccine, mRNA) and the Pfizer-BioNTech COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19) for Use in Individuals 12 Years of Age and Older (revised July 8, 2022).

97. Defendants have knowledge of the '574 patent and knowledge that their actions promoting the use of Comirnaty® in the United States induces infringement and contributorily infringes the '574 patent.

98. Comirnaty® constitutes a material part of the invention claimed in the '574 patent, is especially adopted for use in infringing the claims of the '574 patent, and is not a staple article or commodity of commerce suitable for substantial noninfringing use. Indeed, the only use of Comirnaty® instructed in its package insert infringes the claims of the '574 patent. *See* Ex. 7 at 2 ("COMIRNATY is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.").

99. The ’574 patent is listed on Moderna’s patent marking website for Spikevax®. Pursuant to 35 U.S.C. § 287, Defendants have constructive notice of the ’574 patent through Moderna’s patent marking.

100. Defendants’ infringement of the ’574 patent has been willful. As discussed above, Pfizer and BioNTech chose to advance BNT162b2 as their lead vaccine candidate knowing that it utilized the same chemically-modified mRNA as Moderna’s patent-protected Spikevax®. Defendants have continued to use the invention claimed in the ’574 patent in deliberate disregard for Moderna’s patent rights.

101. Moderna has suffered damages as a result of Defendants’ infringement of the ’574 patent. Moderna is entitled to an award of compensatory damages, including reasonable royalties and/or lost profits, for Defendants’ infringement of the ’574 patent.

102. Defendants have engaged in egregious infringement behavior with respect to the ’574 patent warranting an award of enhanced damages pursuant to 35 U.S.C. § 284.

103. Defendants’ conduct with respect to ’574 patent makes this case stand out from others and warrants an award of attorneys’ fees pursuant to 35 U.S.C. § 285.

COUNT II – INFRINGEMENT OF THE ’600 PATENT

104. Moderna incorporates each of the above paragraphs 1-82 as though fully set forth herein.

105. Upon information and belief, Defendants have directly infringed and continue to directly infringe one or more of the claims of the ’600 patent, either literally or under the doctrine of equivalents, by making, using, selling, offering for sale, and/or importing Comirnaty® in the United States and in this District without authority, in violation of 35 U.S.C. § 271(a).

106. Upon information and belief, the use of Comirnaty® in accordance with its approved package insert and/or emergency use authorization infringes one or more of the claims of

the ’600 patent. Defendants have induced infringement and continue to induce infringement of one or more of the claims of the ’600 patent, either literally or under the doctrine of equivalents, by encouraging others, including but not limited to healthcare providers and patients, to make and use Comirnaty® in the United States and in this District in a manner that would directly infringe the ’600 patent. Defendants have intentionally encouraged and will continue to intentionally encourage acts of direct infringement by others, including but not limited to healthcare providers and patients, with knowledge of the ’600 patent and with knowledge that their acts are encouraging infringement, in violation of 35 U.S.C. § 271(b).

107. Upon information and belief, Comirnaty® constitutes a material part of the invention of one or more claims of the ’600 patent and is not a staple article or commodity of commerce suitable for substantial noninfringing use. Defendants have contributorily infringed and continue to contributorily infringe one or more of the claims of the ’600 patent, either literally or under the doctrine of equivalents, by promoting the making and use of Comirnaty® in accordance with its approved package insert and/or emergency use authorization in the United States and in this District by others, including but not limited to healthcare providers and patients, and knowing that Comirnaty® is especially made or especially adapted for use to infringe the ’600 patent, in violation of 35 U.S.C. § 271(c).

108. Upon information and belief, Defendants have infringed or will infringe one or more of the claims of the ’600 patent, either literally or under the doctrine of equivalents, in violation of 35 U.S.C. § 271(f), including by supplying the global market for Comirnaty® with components, such as mRNA, manufactured in the United States.

109. Comirnaty® satisfies each and every element of one or more claims of the '600 patent. Defendants' actions with respect to Comirnaty® have infringed, induced infringement, or contributorily infringed at least claims 1-2, 4-6, 8-12, 16-17, 20-21, and 26 of the '600 patent.

110. For example, claim 1 of the '600 patent is representative and recites:

> A composition, comprising:
>
> > a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit
> >
> > formulated in a lipid nanoparticle.

111. Comirnaty® is a composition comprising a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit formulated in a lipid nanoparticle.

112. For example, Section 11 of the package insert for Comirnaty® states that "[e]ach 0.3 mL dose of COMIRNATY . . . contains 30 mcg of a nucleoside-modified messenger RNA (mRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2." Ex. 7 at 19. Section 12 of the package insert for Comirnaty® states that "[t]he nucleoside-modified mRNA in COMIRNATY is formulated in lipid particles, which enable delivery of the mRNA into host cells to allow expression of the SARS-CoV-2 S antigen." Ex. 7 at 20. The "SARS-CoV-2 S antigen" encoded by the mRNA in Comirnaty® is a betacoronavirus S protein.

113. Defendants promote the use of Comirnaty® to infringe one or more claims of the '600 patent. For example, Sections 1 and 2 of the package insert for Comirnaty® instruct how to use the vaccine.

114. Defendants further promote the use of Comirnaty® booster shots to infringe one or more claims of the '600 patent. For example, among other things, Pfizer and BioNTech maintain

a website (https://www.comirnaty.com/booster-dose/ [https://perma.cc/7WHG-LZ3B]) that promotes the use of Comirnaty® booster shots in accordance with the FDA's emergency use authorization. Pfizer and BioNTech also provide a "Fact Sheet" that instructs the use of Comirnaty® booster shots to infringe one or more claims of the '600 patent. *See* Ex. 9 at 5.

115. Defendants have knowledge of the '600 patent and knowledge that their actions promoting the use of Comirnaty® in the United States induces infringement and contributorily infringes the '600 patent.

116. Comirnaty® constitutes a material part of the invention claimed in the '600 patent, is especially adopted for use in infringing the claims of the '600 patent, and is not a staple article or commodity of commerce suitable for substantial noninfringing use. Indeed, the only use of Comirnaty® instructed in its package insert infringes the claims of the '600 patent.

117. The '600 patent is listed on Moderna's patent marking website for Spikevax®. Pursuant to 35 U.S.C. § 287, Defendants have constructive notice of the '600 patent through Moderna's patent marking.

118. Defendants' infringement of the '600 patent has been and continues to be willful. As discussed above, Pfizer and BioNTech chose to advance BNT162b2 as their lead vaccine candidate knowing that it utilized the same target antigen as Moderna's patent-protected Spikevax®. Defendants continued to use the invention claimed in the '600 patent in deliberate disregard for Moderna's patent rights.

119. Moderna has suffered damages as a result of Defendants' infringement of the '600 patent. Moderna is entitled to an award of compensatory damages, including reasonable royalties and/or lost profits, for Defendants' infringement of the '600 patent.

120. Defendants have engaged in egregious infringement behavior with respect to the '600 patent warranting an award of enhanced damages pursuant to 35 U.S.C. § 284.

121. Defendants' conduct with respect to '600 patent makes this case stand out from others and warrants an award of attorneys' fees pursuant to 35 U.S.C. § 285.

COUNT III – INFRINGEMENT OF THE '127 PATENT

122. Moderna incorporates each of the above paragraphs 1-82 as though fully set forth herein.

123. Upon information and belief, Defendants have directly infringed and continue to directly infringe one or more of the claims of the '127 patent, either literally or under the doctrine of equivalents, by using Comirnaty® in the United States and in this District, in violation of 35 U.S.C. § 271(a).

124. Upon information and belief, the use of Comirnaty® in accordance with its approved package insert and/or emergency use authorization infringes one or more of the claims of the '127 patent. Defendants have induced infringement and continue to induce infringement of one or more of the claims of the '127 patent, either literally or under the doctrine of equivalents, by encouraging others, including but not limited to healthcare providers and patients, to make and use Comirnaty® in the United States and in this District in a manner that would directly infringe the '127 patent. Defendants have intentionally encouraged and will continue to intentionally encourage acts of direct infringement by others, including but not limited to healthcare providers and patients, with knowledge of the '127 patent and with knowledge that their acts are encouraging infringement, in violation of 35 U.S.C. § 271(b).

125. Upon information and belief, Comirnaty® constitutes a material part of the invention of one or more claims of the '127 patent and is not a staple article or commodity of commerce suitable for substantial noninfringing use. Defendants have contributorily infringed and continue

to contributorily infringe one or more of the claims of the '127 patent, either literally or under the doctrine of equivalents, by promoting the making and use of Comirnaty® in accordance with its approved package insert and/or emergency use authorization in the United States and in this District by others, including but not limited to healthcare providers and patients, and knowing that Comirnaty® is especially made or especially adapted for use to infringe the '127 patent, in violation of 35 U.S.C. § 271(c).

126. Upon information and belief, Defendants have infringed or will infringe one or more of the claims of the '127 patent, either literally or under the doctrine of equivalents, in violation of 35 U.S.C. § 271(f), including by supplying the global market for Comirnaty® with components, such as mRNA, manufactured in the United States.

127. The use of Comirnaty® as instructed in its package insert satisfies each and every element of one or more claims of the '127 patent. Upon information and belief, Defendants and others, including but not limited to healthcare providers and patients, have used Comirnaty® in the United States and in this District as instructed in Comirnaty®'s package insert to practice the methods claimed in the '127 patent. Defendants' actions with respect to Comirnaty® have infringed, induced infringement, or contributorily infringed at least claims 1-3, 6-9, 11-13, 17-18, and 20 of the '127 patent.

128. For example, claim 1 of the '127 patent is representative and recites:

> A method comprising administering to a subject
>
> > a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit
> >
> > formulated in a lipid nanoparticle
> >
> > in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit

> wherein the lipid nanoparticle comprises 20-60 mol% ionizable cationic lipid, 5-25 mol% neutral lipid, 25-55 mol% cholesterol, and 0.5-15 mol% PEG-modified lipid.

129. The use of Comirnaty® as instructed in its package insert is a method comprising administering to a subject a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit formulated in a lipid nanoparticle in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit wherein the lipid nanoparticle comprises 20-60 mol% ionizable cationic lipid, 5-25 mol% neutral lipid, 25-55 mol% cholesterol, and 0.5-15 mol% PEG-modified lipid.

130. For example, Section 2.2 of the package insert for Comirnaty® instructs users to "[a]dminister a single 0.3 mL dose of COMIRNATY intramuscularly." Ex. 7 at 6. Section 11 of the package insert for Comirnaty® states that "[e]ach 0.3 mL dose of COMIRNATY . . . contains 30 mcg of a nucleoside-modified messenger RNA (mRNA) encoding the viral spike (S) glycoprotein SARS-CoV-2." Ex. 7 at 19. Section 12 of the package insert for Comirnaty® states that "[t]he nucleoside-modified mRNA in COMIRNATY is formulated in lipid particles, which enable delivery of the mRNA into host cells to allow expression of the SARS-CoV-2 S antigen." Ex. 7 at 20. The "SARS-CoV-2 S antigen" encoded by the mRNA in Comirnaty® is a betacoronavirus S protein. Section 12 of the package insert for Comirnaty® further states that "[t]he vaccine elicits an immune response to the S antigen, which protects against COVID-19." *Id.* Section 11 of the package insert for Comirnaty® further states that "[e]ach 0.3 mL dose of the COMIRNATY . . . also includes the following ingredients: lipids (0.43 mg ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2-(polyethylene glycol 2000)-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potas-

sium chloride, 0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose." Ex. 7 at 19-20. The lipid nanoparticle composition of Comirnaty® falls within the ranges specified in the claims of the '127 patent.

131. The use of Comirnaty® booster shots pursuant to Pfizer and BioNTech's emergency use authorization infringes the claims of the '127 patent for the same reasons. For example, Pfizer and BioNTech have published a "Fact Sheet" that instructs the use of booster shots in individuals 12 years of age or older who have completed their primary vaccination series and explains that Pfizer and BioNTech's vaccine "has been shown to prevent COVID-19." Ex. 9 at 5. Booster doses are identical in dosage strength and composition to doses of the primary vaccination series of Comirnaty®. *See* Press Release, Pfizer and BioNTech Announce Phase 3 Trial Data Showing High Efficacy of a Booster Dose of Their COVID-19 Vaccine (Oct. 21, 2021), https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-phase-3-trial-data-showing [https://perma.cc/94KH-8R2B].

132. Defendants have knowledge of the '127 patent and knowledge that their actions promoting the use of Comirnaty® in the United States induces infringement and contributorily infringes the '127 patent.

133. Comirnaty® constitutes a material part of the invention claimed in the '127 patent, is especially adopted for use in infringing the claims of the '127 patent, and is not a staple article or commodity of commerce suitable for substantial noninfringing use. Indeed, the only use of Comirnaty® instructed in its package insert infringes the claims of the '127 patent.

134. Defendants' infringement of the '127 patent has been willful. As discussed above, Pfizer and BioNTech chose to advance BNT162b2 as their lead vaccine candidate knowing that it utilized the same target antigen as Moderna's patent-protected Spikevax®. Defendants continue

to promote the use the invention claimed in the '127 patent in deliberate disregard for Moderna's patent rights.

135. Moderna has suffered damages as a result of Defendants' infringement of the '127 patent. Moderna is entitled to an award of compensatory damages, including reasonable royalties and/or lost profits, for Defendants' infringement of the '127 patent.

136. Defendants have engaged in egregious infringement behavior with respect to the '127 patent warranting an award of enhanced damages pursuant to 35 U.S.C. § 284.

137. Defendants' conduct with respect to '127 patent makes this case stand out from others and warrants an award of attorneys' fees pursuant to 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Moderna prays that this Court grant the following relief:

a. A judgment that Defendants have infringed one or more claims of the Asserted Patents, induced infringement of one or more claims of the Asserted Patents, and/or contributorily infringed one of more claims of the Asserted Patents;

b. A judgment that Defendants' infringement is willful;

c. An award to Moderna of monetary damages for Defendants' infringement occurring on or after March 8, 2022 other than for sales to the U.S. government that are subject to 28 U.S.C. § 1498 or to the 92 low- and middle-income countries in the Gavi COVAX Advance Market Commitment (AMC), including reasonable royalties and/or lost profits, together with interest, costs, expenses, disbursements, and an accounting and/or ongoing royalty for any post-judgment infringement;

d. An award to Moderna of all other damages permitted by 35 U.S.C. § 284, including enhanced damages up to three times the amount of compensatory damages found;

e. A declaration that this is an exceptional case and an award to Moderna of its attorneys' fees, costs, and expenses, pursuant to 35 U.S.C. § 285; and

f. Such other relief as this Court may deem just and proper, except Moderna does not seek injunctive relief against Comirnaty®.

DEMAND FOR JURY TRIAL

Moderna respectfully requests a trial by jury on all issues so triable in accordance with Rule 38 of the Federal Rules of Civil Procedure.

Date: August 26, 2022

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EXHIBIT 1

US010898574B2

(12) **United States Patent**
de Fougerolles et al.

(10) **Patent No.: US 10,898,574 B2**
(45) **Date of Patent: *Jan. 26, 2021**

(54) **DELIVERY AND FORMULATION OF ENGINEERED NUCLEIC ACIDS**

(71) Applicant: **ModernaTX, Inc.**, Cambridge, MA (US)

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(73) Assignee: **ModernaTX, Inc.**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **15/927,730**

(22) Filed: **Mar. 21, 2018**

(65) **Prior Publication Data**

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Related U.S. Application Data

(60) Continuation of application No. 15/379,284, filed on Dec. 14, 2016, now Pat. No. 9,950,068, which is a division of application No. 14/337,513, filed on Jul. 22, 2014, now Pat. No. 9,533,047, which is a continuation of application No. 13/897,362, filed on May 18, 2013, now abandoned, which is a continuation of application No. 13/437,034, filed on Apr. 2, 2012, now Pat. No. 8,710,200.

(60) Provisional application No. 61/470,451, filed on Mar. 31, 2011.

(51) **Int. Cl.**

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A61K 38/19	(2006.01)
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C12N 15/67	(2006.01)
C12N 15/87	(2006.01)
C12N 9/64	(2006.01)
A61K 48/00	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 47/18*** (2013.01); ***A61K 31/7088*** (2013.01); ***A61K 31/7115*** (2013.01); ***A61K 38/193*** (2013.01); ***A61K 38/4846*** (2013.01); ***A61K 47/22*** (2013.01); ***A61K 47/28*** (2013.01); ***C07K 14/535*** (2013.01); ***C12N 9/644*** (2013.01); ***C12N 15/67*** (2013.01); ***C12N 15/87*** (2013.01); *A61K 48/00* (2013.01); *C12N 2310/335* (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

Provided are formulations, compositions and methods for delivering biological moieties such as modified nucleic acids into cells to modulate protein expression. Such compositions and methods include the delivery of biological moieties, and are useful for production of proteins.

10 Claims, 20 Drawing Sheets

Specification includes a Sequence Listing.

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WO	WO-2014/152211	A1	9/2014
WO	WO-2014/152513	A1	9/2014
WO	WO-2014/152540	A1	9/2014
WO	WO-2014/152659	A1	9/2014
WO	WO-2014/152673	A1	9/2014
WO	WO-2014/164253	A1	10/2014
WO	WO-2015/006747	A2	1/2015
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WO	WO-2015/034928	A1	3/2015
WO	WO-2015/038892	A1	3/2015
WO	WO-2015/048744	A2	4/2015
WO	WO-2015/051169	A2	4/2015
WO	WO-2015/051173	A2	4/2015
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WO	WO-2015/101416	A1	7/2015
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WO	WO-2015/196128	A2	12/2015
WO	WO-2015/196130	A2	12/2015
WO	WO-2016/010840	A1	1/2016
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WO	WO-2016/011226	A1	1/2016
WO	WO-2016/034620	A1	3/2016
WO	WO-2016/036902	A1	3/2016
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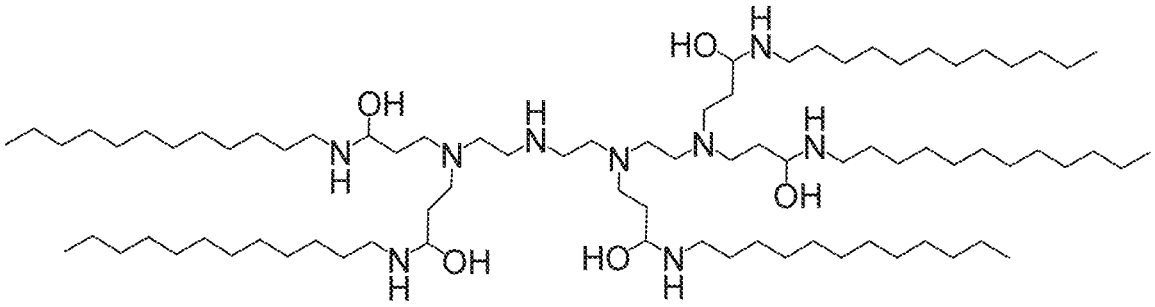
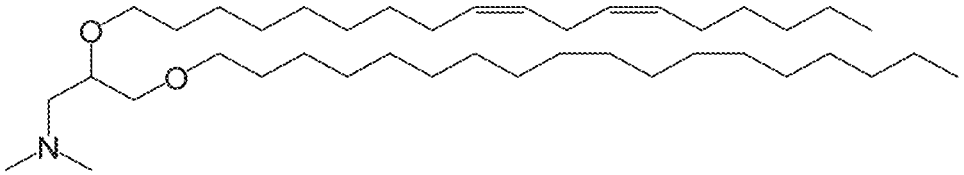
FIG. 1

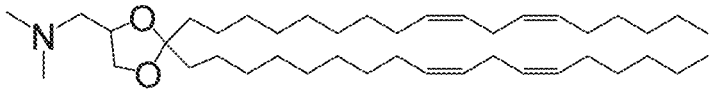
98N12-5 (TETA5-LAP)



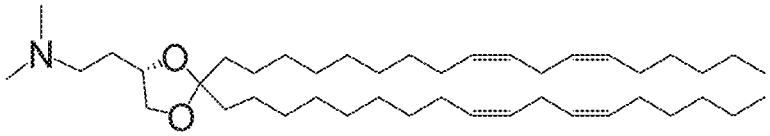
DLin DMA



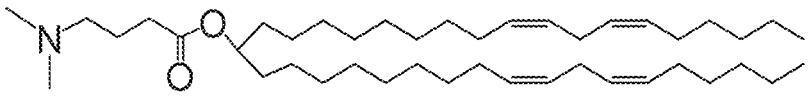
DLin-K-DMA (2,2-Dilinoleyl-4-dimethylaminomethyl-[1,3]-dioxolane)



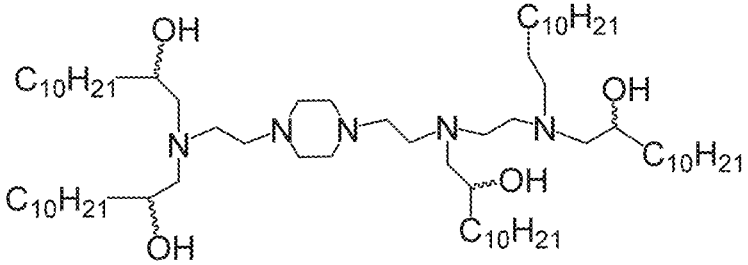
DLin-KC2-DMA



DLin-MC3-DMA



C12-200



PRIOR ART

FIG. 2

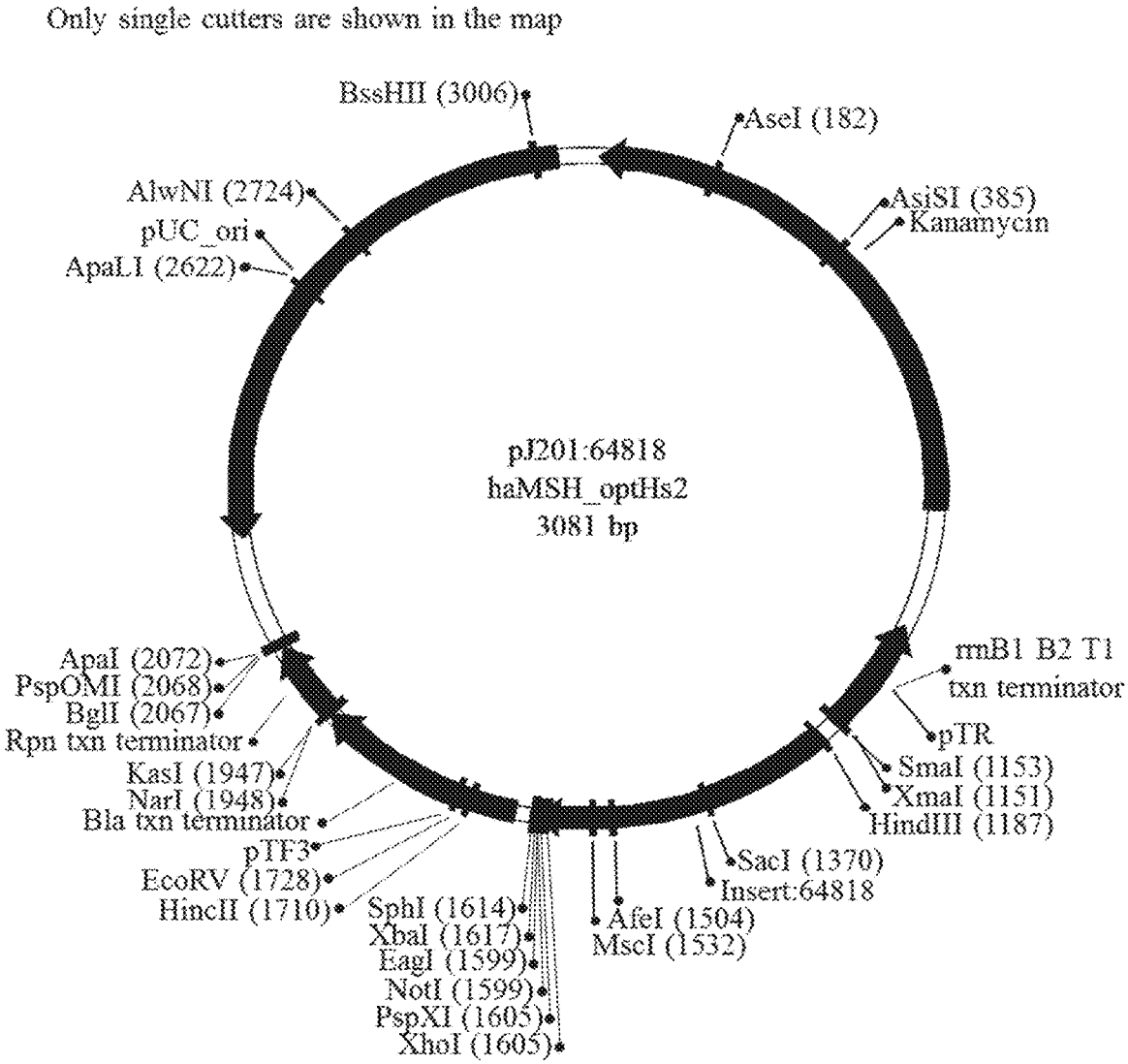

Only single cutters are shown in the map
BssHII (3006)
AseI (182)
AlwNI (2724)
pUC_ori
ApaLI (2622)
AsiSI (385)
Kanamycin
pJ201:64818
haMSH_optHs2
3081 bp
rrnB1 B2 T1
txn terminator
pTR
SmaI (1153)
XmaI (1151)
HindIII (1187)
SacI (1370)
Insert:64818
AfeI (1504)
MscI (1532)
ApaI (2072)
PspOMI (2068)
BglI (2067)
Rpn txn terminator
KasI (1947)
NarI (1948)
Bla txn terminator
pTF3
EcoRV (1728)
HincII (1710)
SphI (1614)
XbaI (1617)
EagI (1599)
NotI (1599)
PspXI (1605)
XhoI (1605)

FIG. 3A

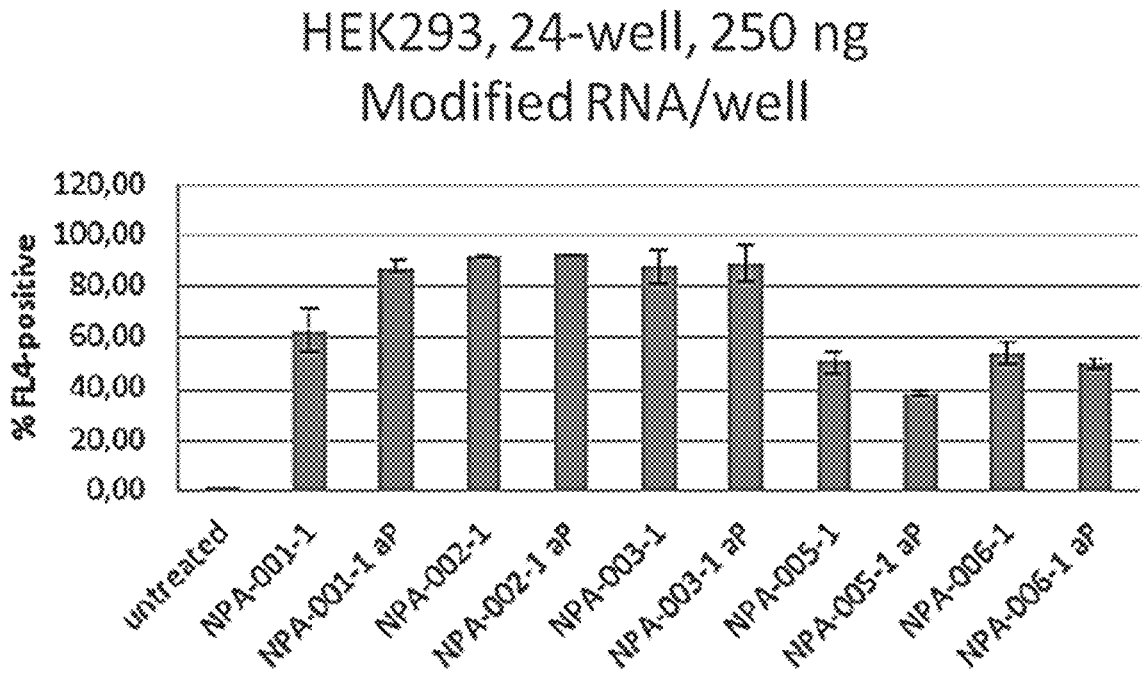

HEK293, 24-well, 250 ng
Modified RNA/well
% FL4-positive
120,00
100,00
80,00
60,00
40,00
20,00
0,00
untreated
NPA-001-1
NPA-001-1 aP
NPA-002-1
NPA-002-1 aP
NPA-003-1
NPA-003-1 aP
NPA-005-1
NPA-005-1 aP
NPA-006-1
NPA-006-1 aP

FIG. 3B

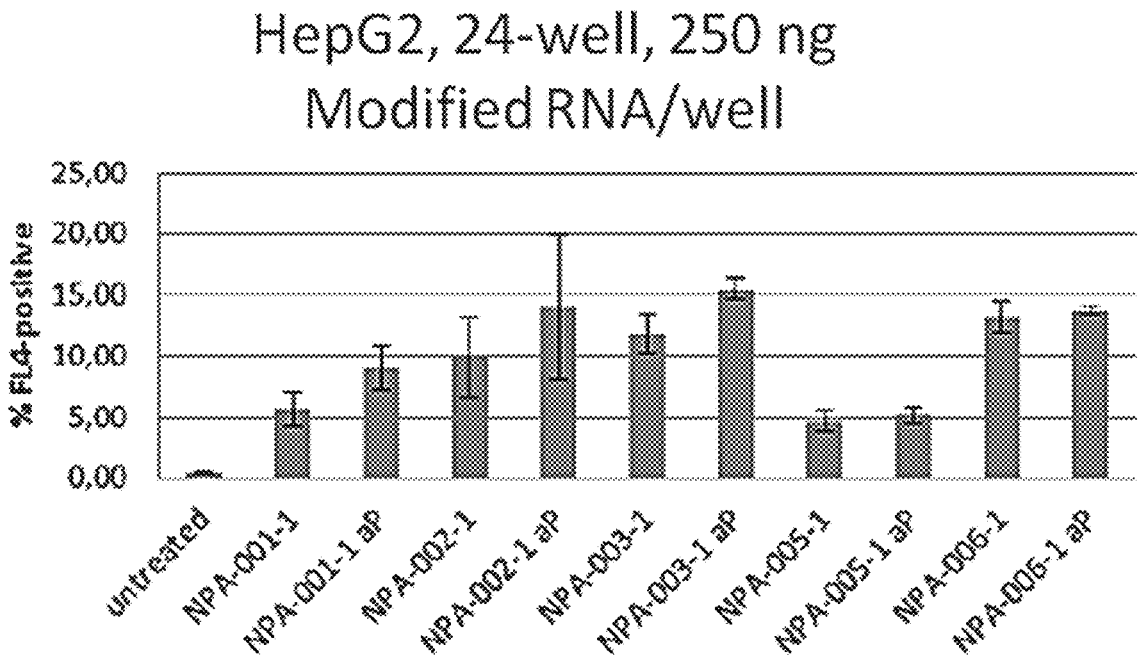

HepG2, 24-well, 250 ng
Modified RNA/well
% FL4-positive
25,00
20,00
15,00
10,00
5,00
0,00
untreated
NPA-001-1
NPA-001-1 aP
NPA-002-1
NPA-002-1 aP
NPA-003-1
NPA-003-1 aP
NPA-005-1
NPA-005-1 aP
NPA-006-1
NPA-006-1 aP

FIG. 4A

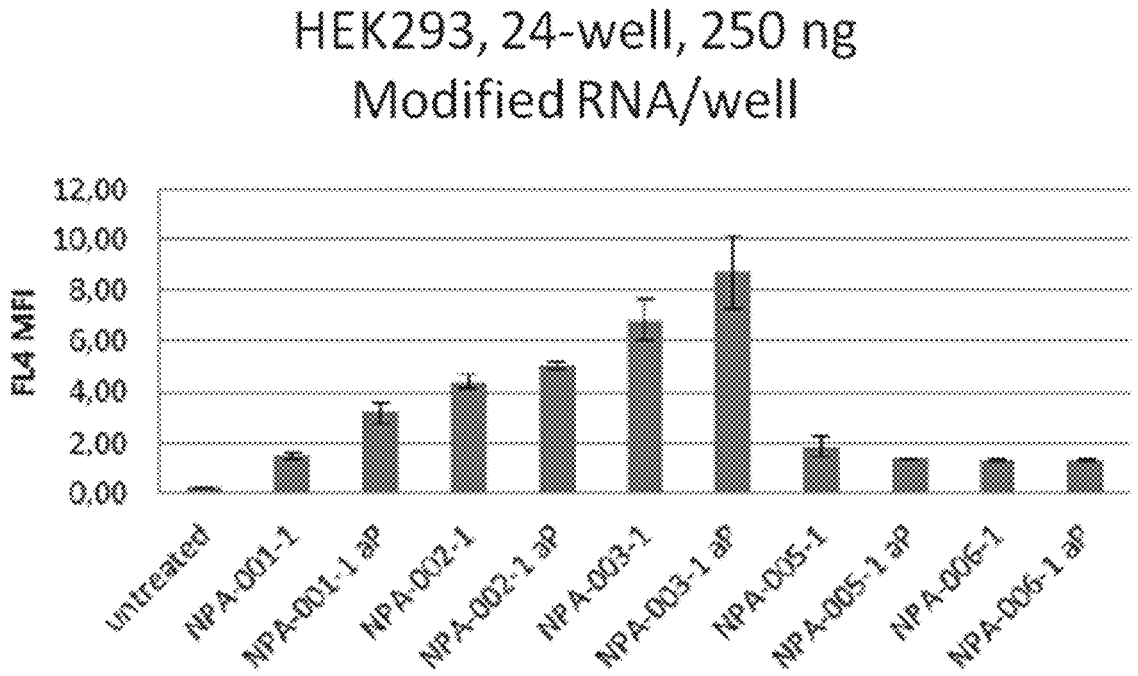

HEK293, 24-well, 250 ng
Modified RNA/well
FL4 MFI
12,00
10,00
8,00
6,00
4,00
2,00
0,00
untreated
NPA-001-1
NPA-001-1 aP
NPA-002-1
NPA-002-1 aP
NPA-003-1
NPA-003-1 aP
NPA-005-1
NPA-005-1 aP
NPA-006-1
NPA-006-1 aP

FIG. 4B

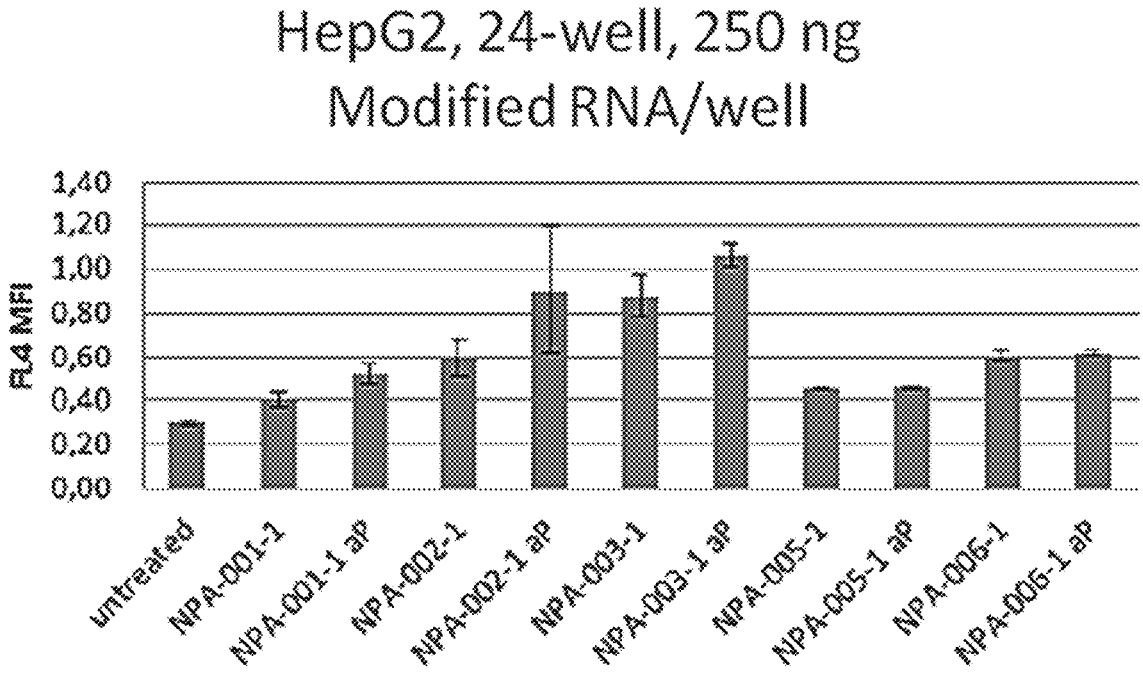

HepG2, 24-well, 250 ng
Modified RNA/well
FL4 MFI
1,40
1,20
1,00
0,80
0,60
0,40
0,20
0,00
untreated
NPA-001-1
NPA-001-1 aP
NPA-002-1
NPA-002-1 aP
NPA-003-1
NPA-003-1 aP
NPA-005-1
NPA-005-1 aP
NPA-006-1
NPA-006-1 aP

FIG. 5A

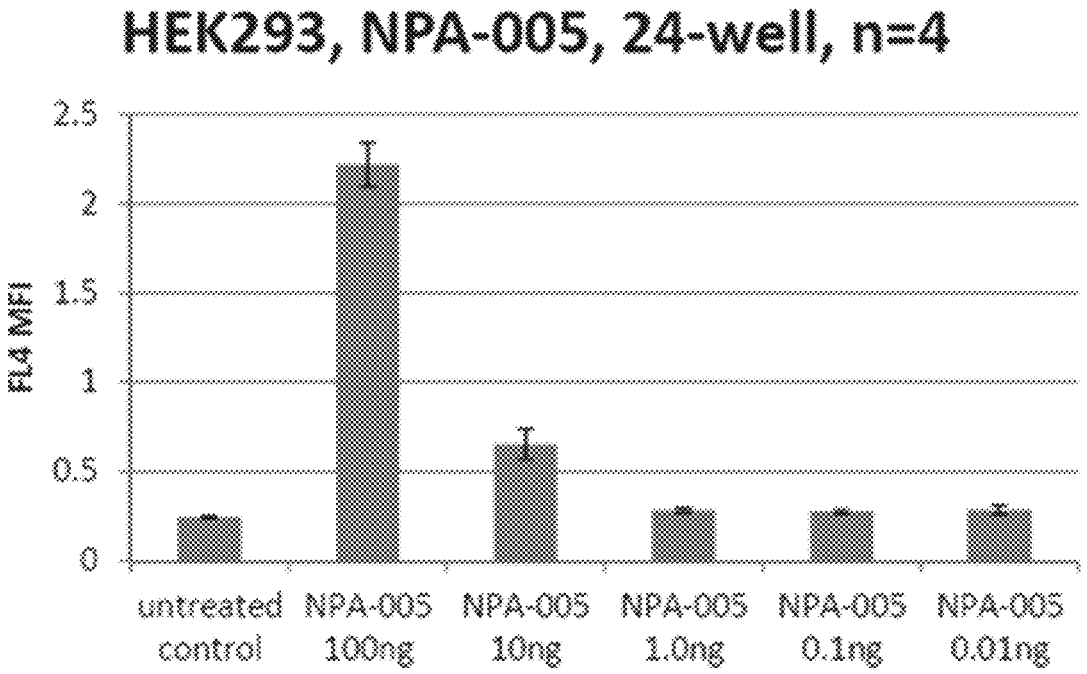

HEK293, NPA-005, 24-well, n=4
FL4 MFI
2.5
2
1.5
1
0.5
0
untreated control
NPA-005 100ng
NPA-005 10ng
NPA-005 1.0ng
NPA-005 0.1ng
NPA-005 0.01ng

FIG. 5B

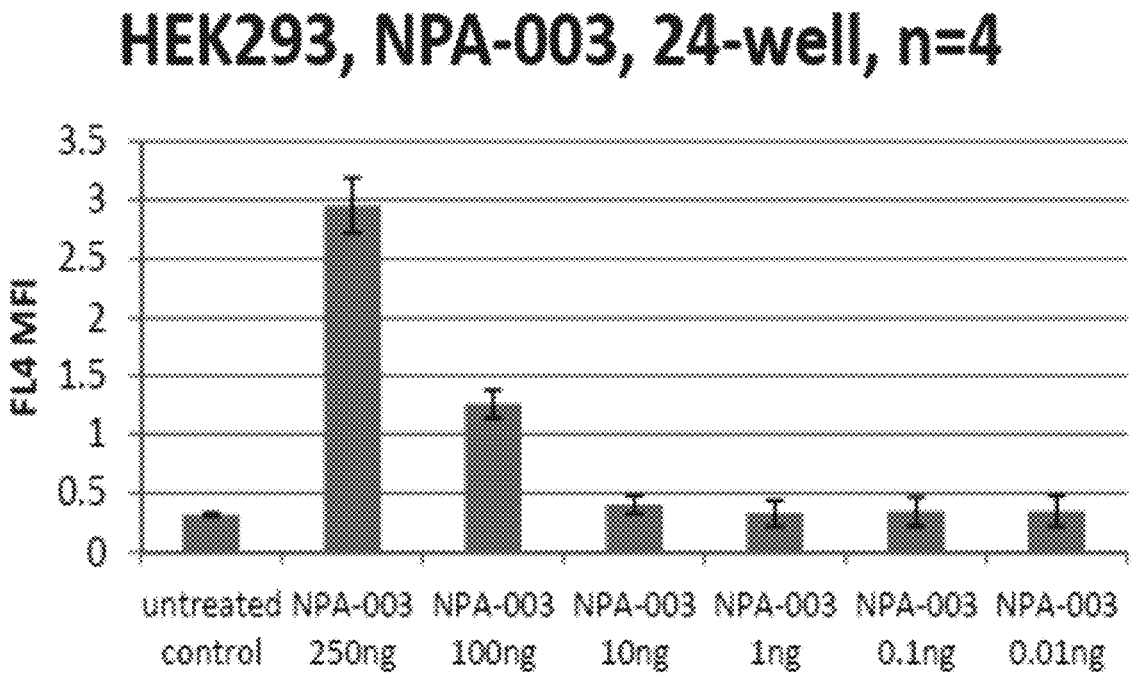

HEK293, NPA-003, 24-well, n=4
FL4 MFI
3.5
3
2.5
2
1.5
1
0.5
0
untreated control
NPA-003 250ng
NPA-003 100ng
NPA-003 10ng
NPA-003 1ng
NPA-003 0.1ng
NPA-003 0.01ng

FIG. 5C

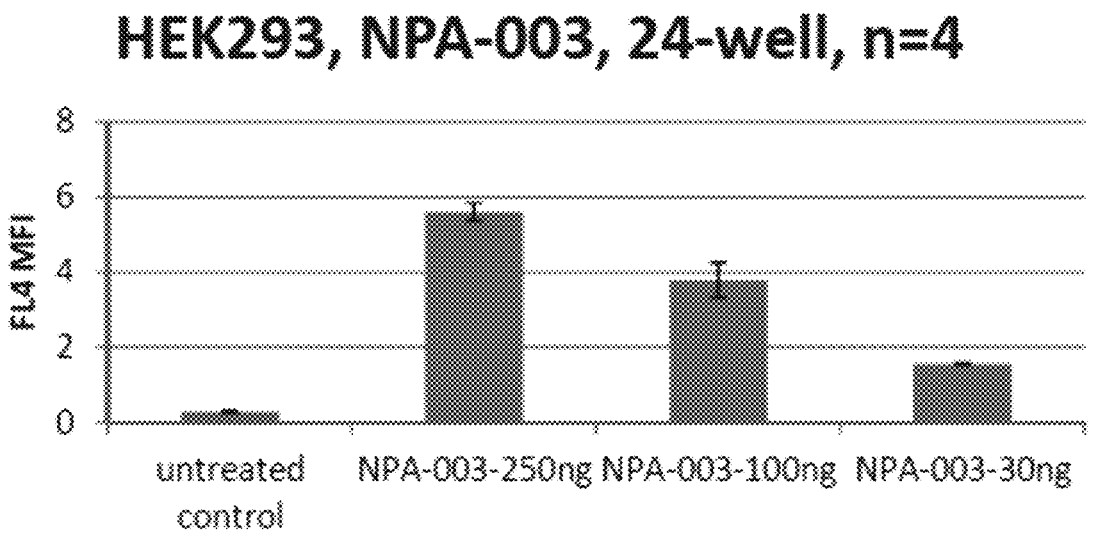

HEK293, NPA-003, 24-well, n=4
FL4 MFI
8
6
4
2
0
untreated control
NPA-003-250ng
NPA-003-100ng
NPA-003-30ng

FIG. 6A

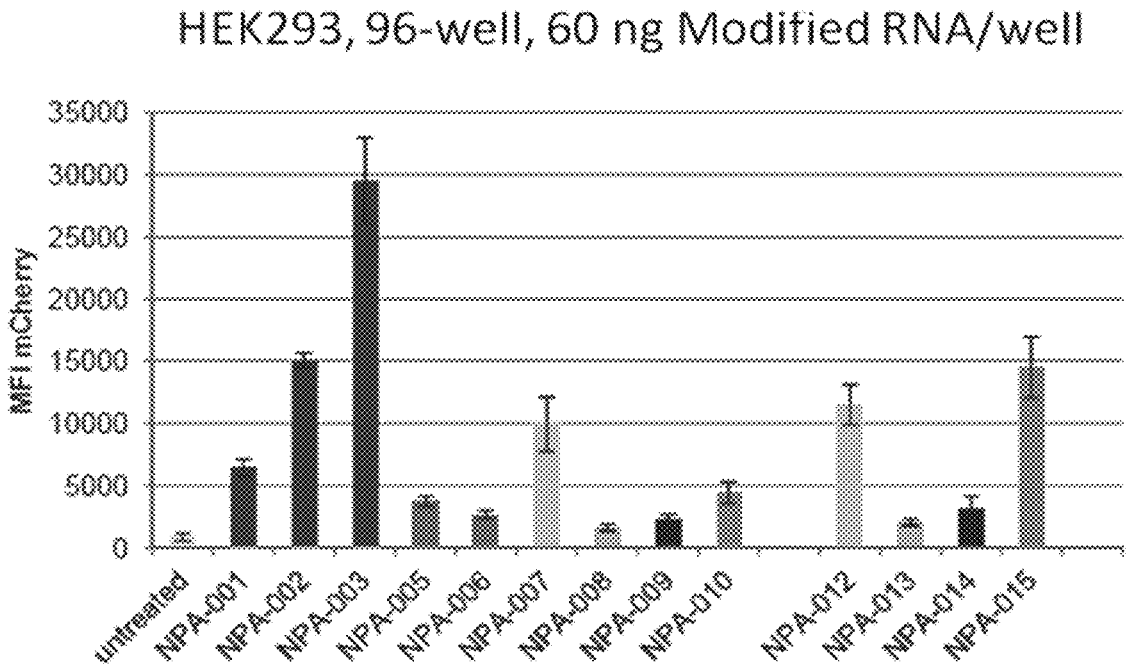

HEK293, 96-well, 60 ng Modified RNA/well
MFI mCherry
35000
30000
25000
20000
15000
10000
5000
0
untreated
NPA-001
NPA-002
NPA-003
NPA-005
NPA-006
NPA-007
NPA-008
NPA-009
NPA-010
NPA-012
NPA-013
NPA-014
NPA-015

FIG. 6B

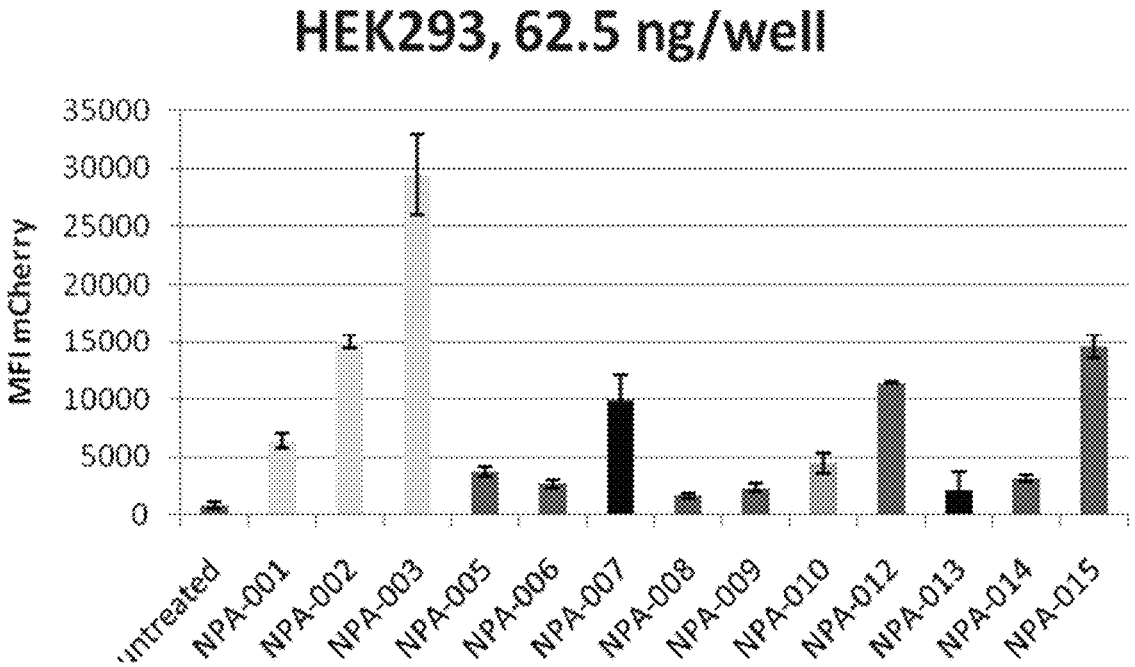

HEK293, 62.5 ng/well
MFI mCherry
35000
30000
25000
20000
15000
10000
5000
0
untreated
NPA-001
NPA-002
NPA-003
NPA-005
NPA-006
NPA-007
NPA-008
NPA-009
NPA-010
NPA-012
NPA-013
NPA-014
NPA-015

FIG. 6C

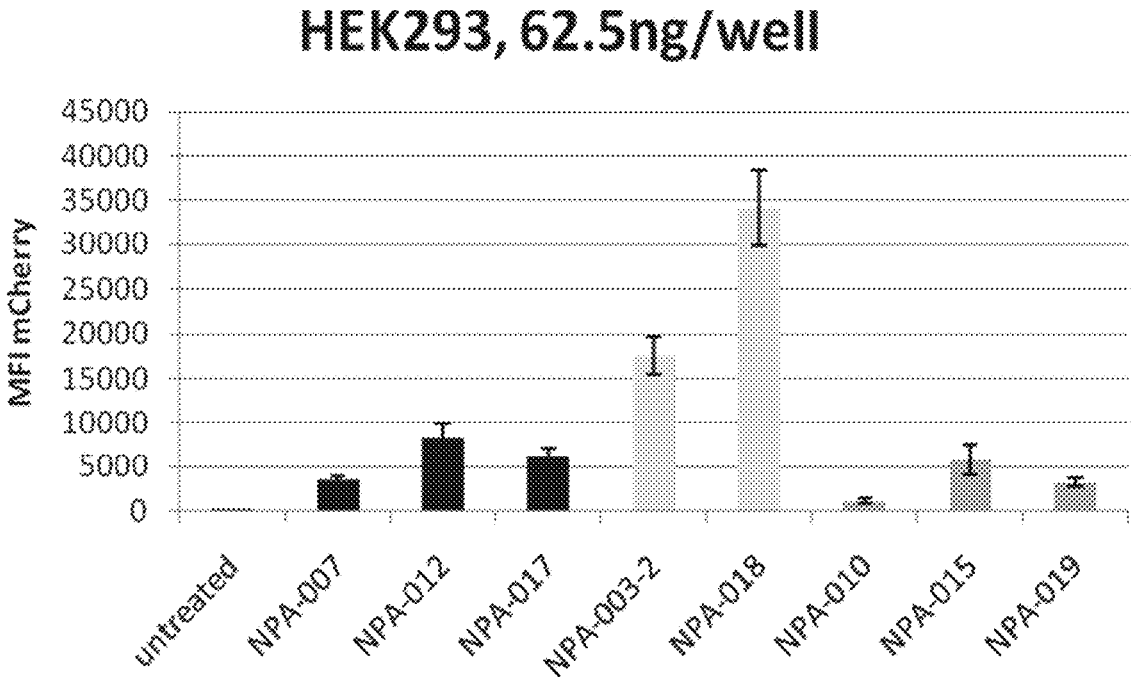

HEK293, 62.5ng/well
MFI mCherry
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
untreated
NPA-007
NPA-012
NPA-017
NPA-003-2
NPA-018
NPA-010
NPA-015
NPA-019

FIG. 6D

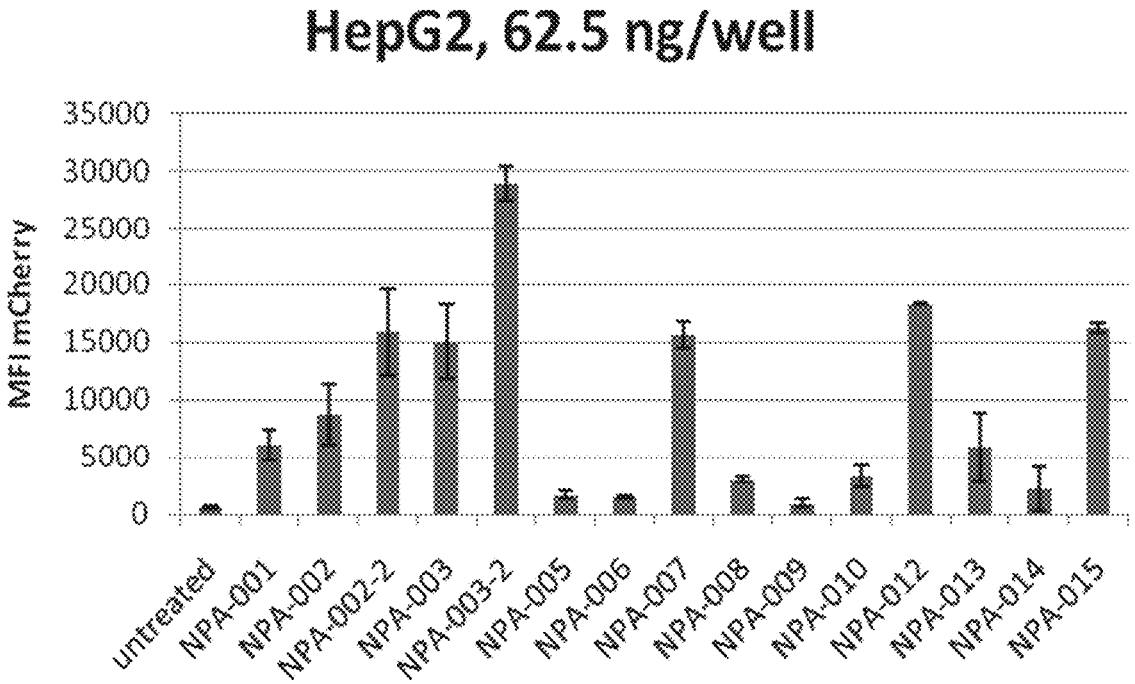

HepG2, 62.5 ng/well
MFI mCherry
35000
30000
25000
20000
15000
10000
5000
0
untreated
NPA-001
NPA-002
NPA-002-2
NPA-003
NPA-003-2
NPA-005
NPA-006
NPA-007
NPA-008
NPA-009
NPA-010
NPA-012
NPA-013
NPA-014
NPA-015

FIG. 6E

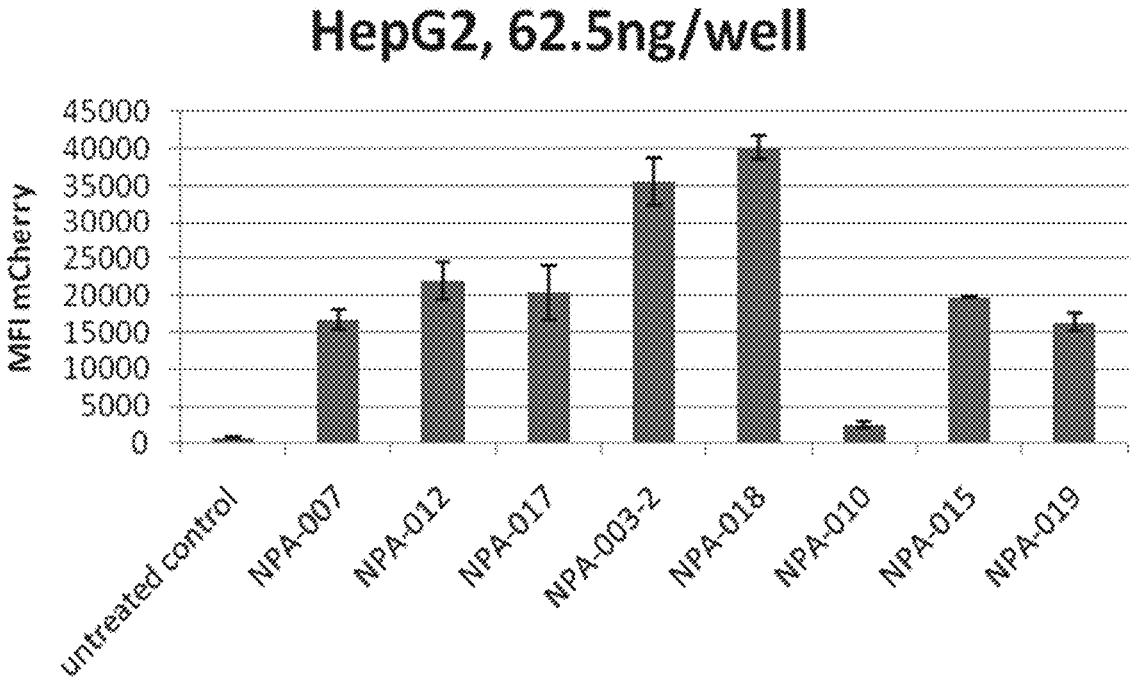

HepG2, 62.5ng/well
MFI mCherry
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
untreated control
NPA-007
NPA-012
NPA-017
NPA-003-2
NPA-018
NPA-010
NPA-015
NPA-019

FIG. 7A

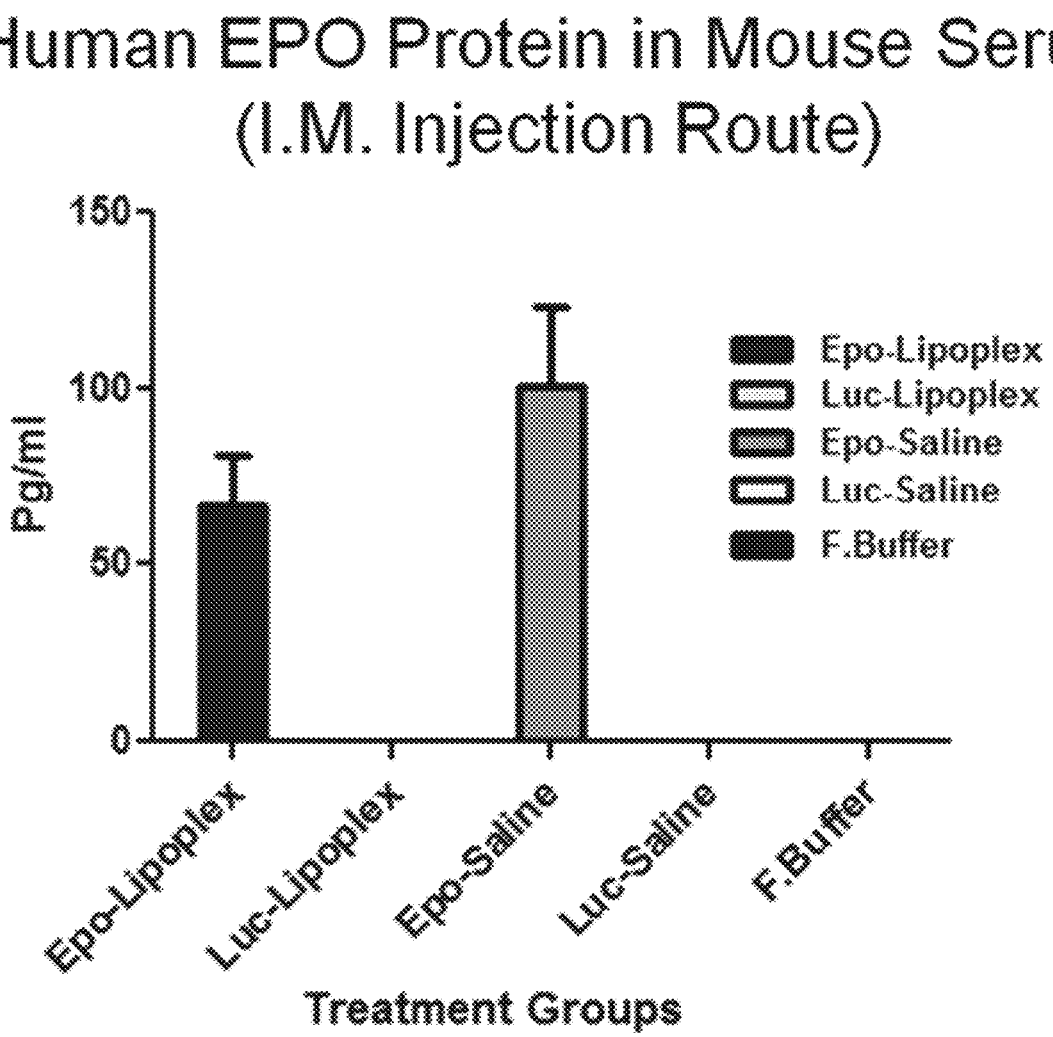

Human EPO Protein in Mouse Serum
(I.M. Injection Route)
150
100
50
0
Pg/ml
Epo-Lipoplex
Luc-Lipoplex
Epo-Saline
Luc-Saline
F.Buffer
Epo-Lipoplex
Luc-Lipoplex
Epo-Saline
Luc-Saline
F.Buffer
Treatment Groups

FIG. 7B

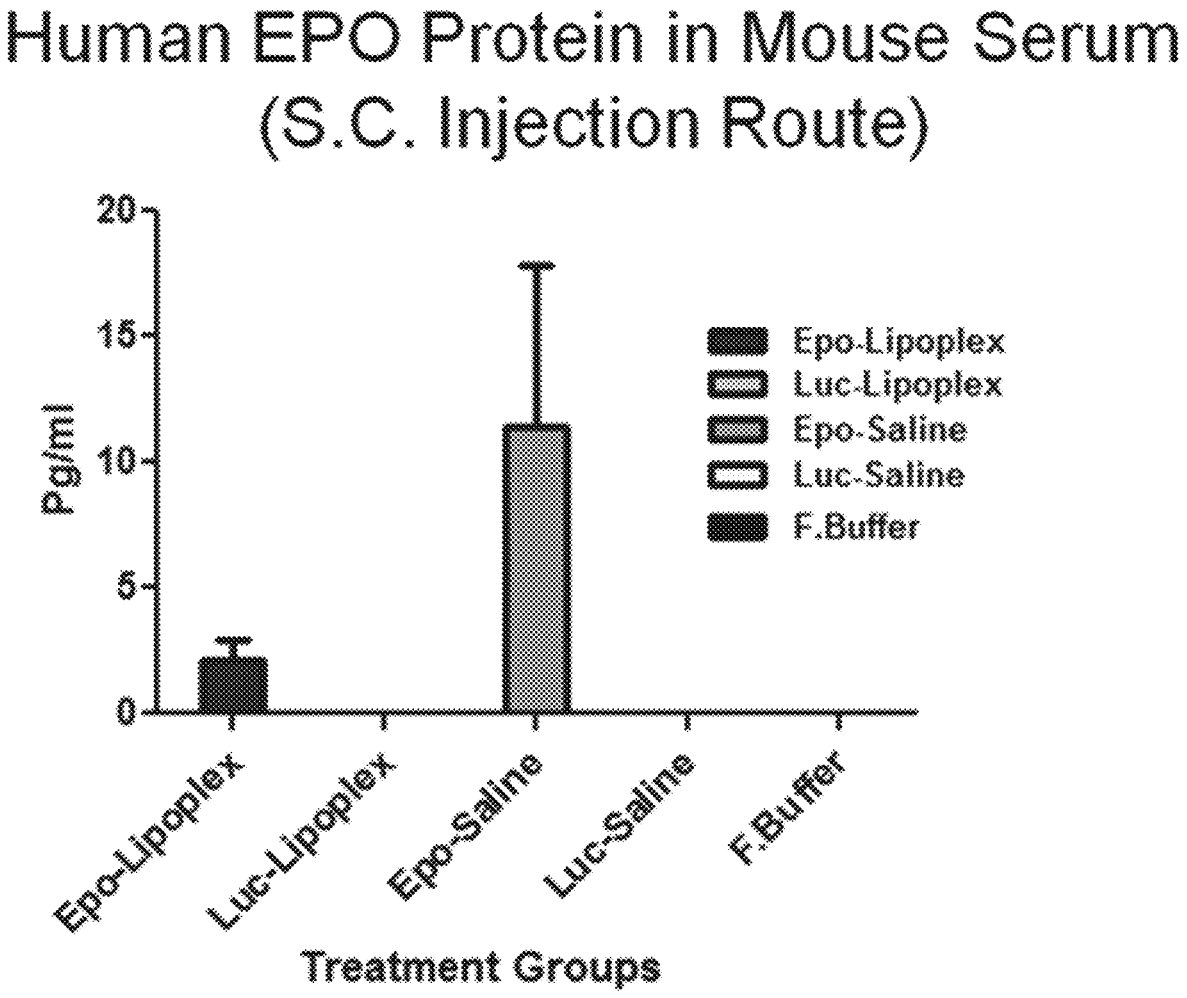

Human EPO Protein in Mouse Serum
(S.C. Injection Route)
Pg/ml
20
15
10
5
0
Epo-Lipoplex
Luc-Lipoplex
Epo-Saline
Luc-Saline
F.Buffer
Epo-Lipoplex
Luc-Lipoplex
Epo-Saline
Luc-Saline
F.Buffer
Treatment Groups

FIG. 8A

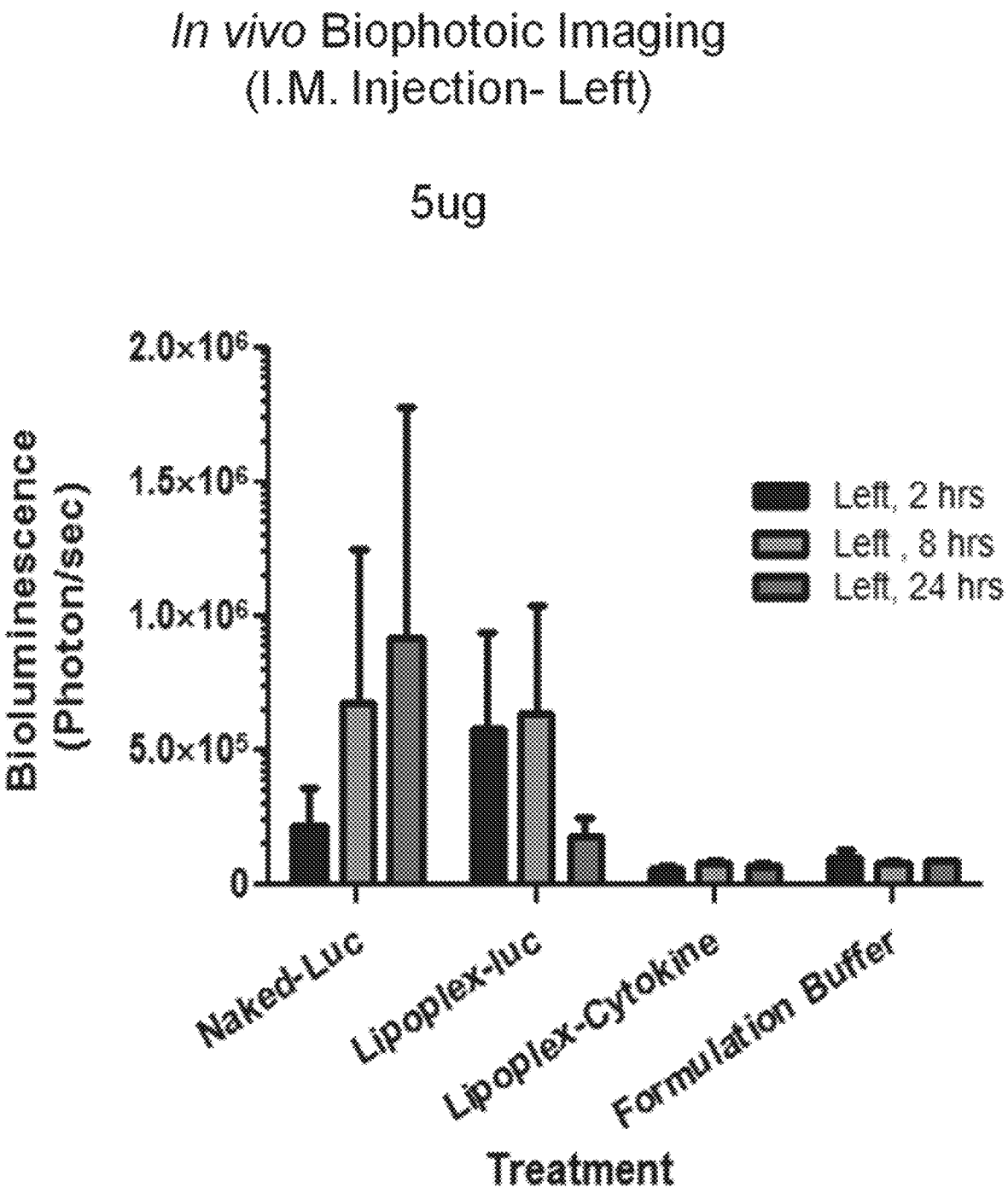

In vivo Biophotoic Imaging
(I.M. Injection- Left)
5ug
Bioluminescence (Photon/sec)
2.0×10⁶
1.5×10⁶
1.0×10⁶
5.0×10⁵
0
Left, 2 hrs
Left , 8 hrs
Left, 24 hrs
Naked-Luc
Lipoplex-luc
Lipoplex-Cytokine
Formulation Buffer
Treatment

FIG. 8B

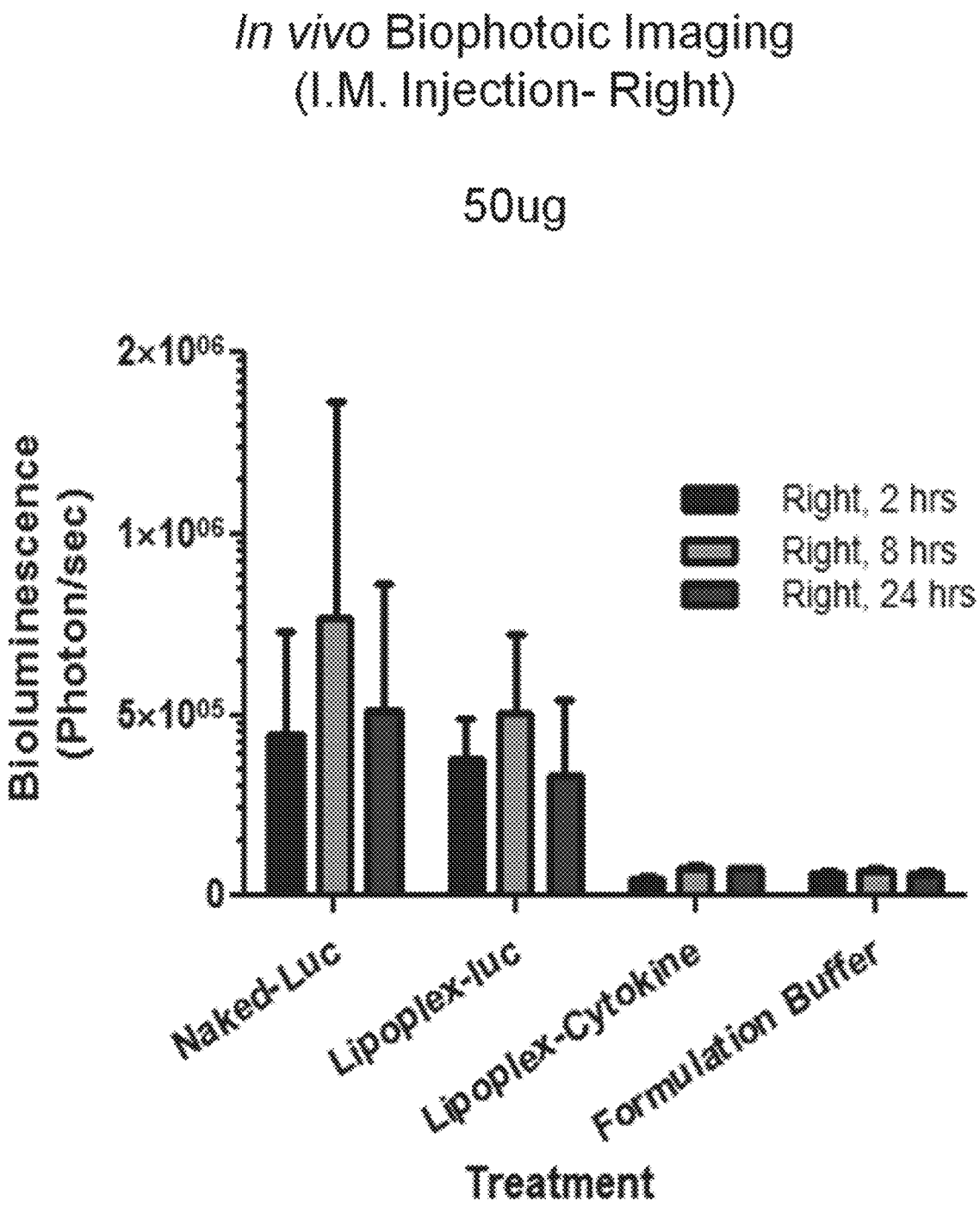

In vivo Biophotoic Imaging
(I.M. Injection- Right)
50ug
Bioluminescence (Photon/sec)
2×10^06
1×10^06
5×10^05
0
Right, 2 hrs
Right, 8 hrs
Right, 24 hrs
Naked-Luc
Lipoplex-luc
Lipoplex-Cytokine
Formulation Buffer
Treatment

FIG. 8C

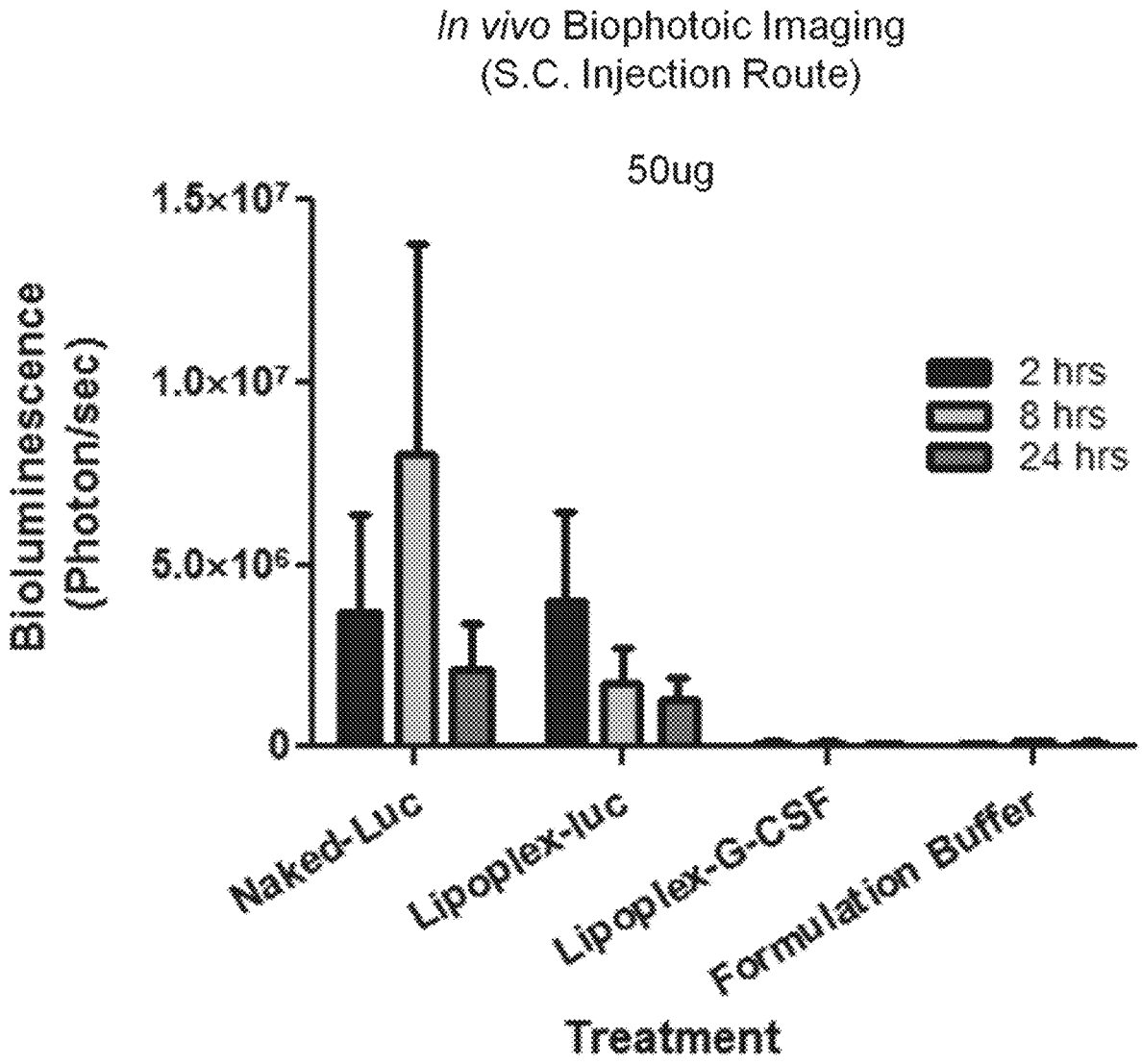

In vivo Biophotoic Imaging
(S.C. Injection Route)
50ug
Bioluminescence (Photon/sec)
1.5×10⁷
1.0×10⁷
5.0×10⁶
0
2 hrs
8 hrs
24 hrs
Naked-Luc
Lipoplex-luc
Lipoplex-G-CSF
Formulation Buffer
Treatment

FIG. 8D

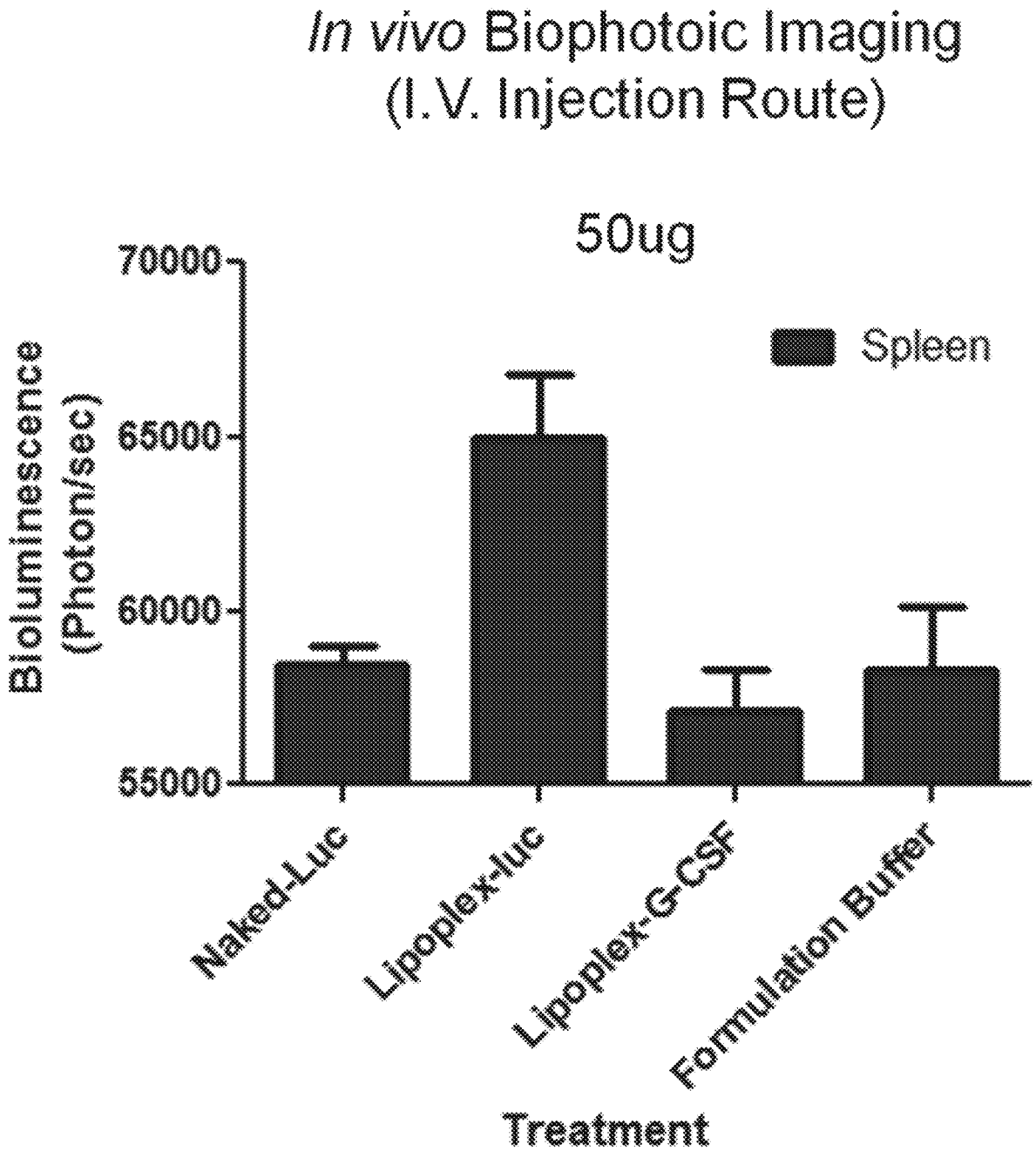
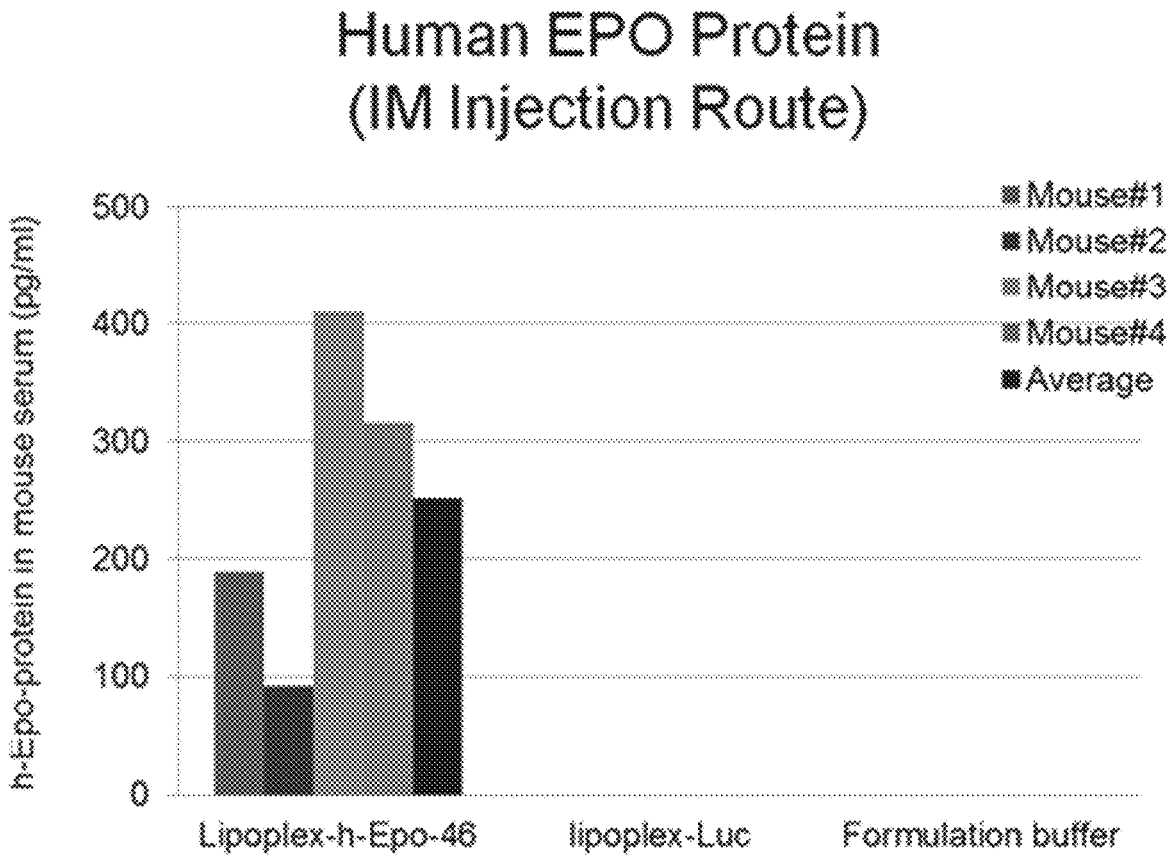

In vivo Biophotoic Imaging
(I.V. Injection Route)
50ug
Spleen
Bioluminescence (Photon/sec)
70000
65000
60000
55000
Naked-Luc
Lipoplex-luc
Lipoplex-G-CSF
Formulation Buffer
Treatment

FIG. 9


Human EPO Protein
(IM Injection Route)
h-Epo-protein in mouse serum (pg/ml)
500
400
300
200
100
0
Mouse#1
Mouse#2
Mouse#3
Mouse#4
Average
Lipoplex-h-Epo-46
lipoplex-Luc
Formulation buffer

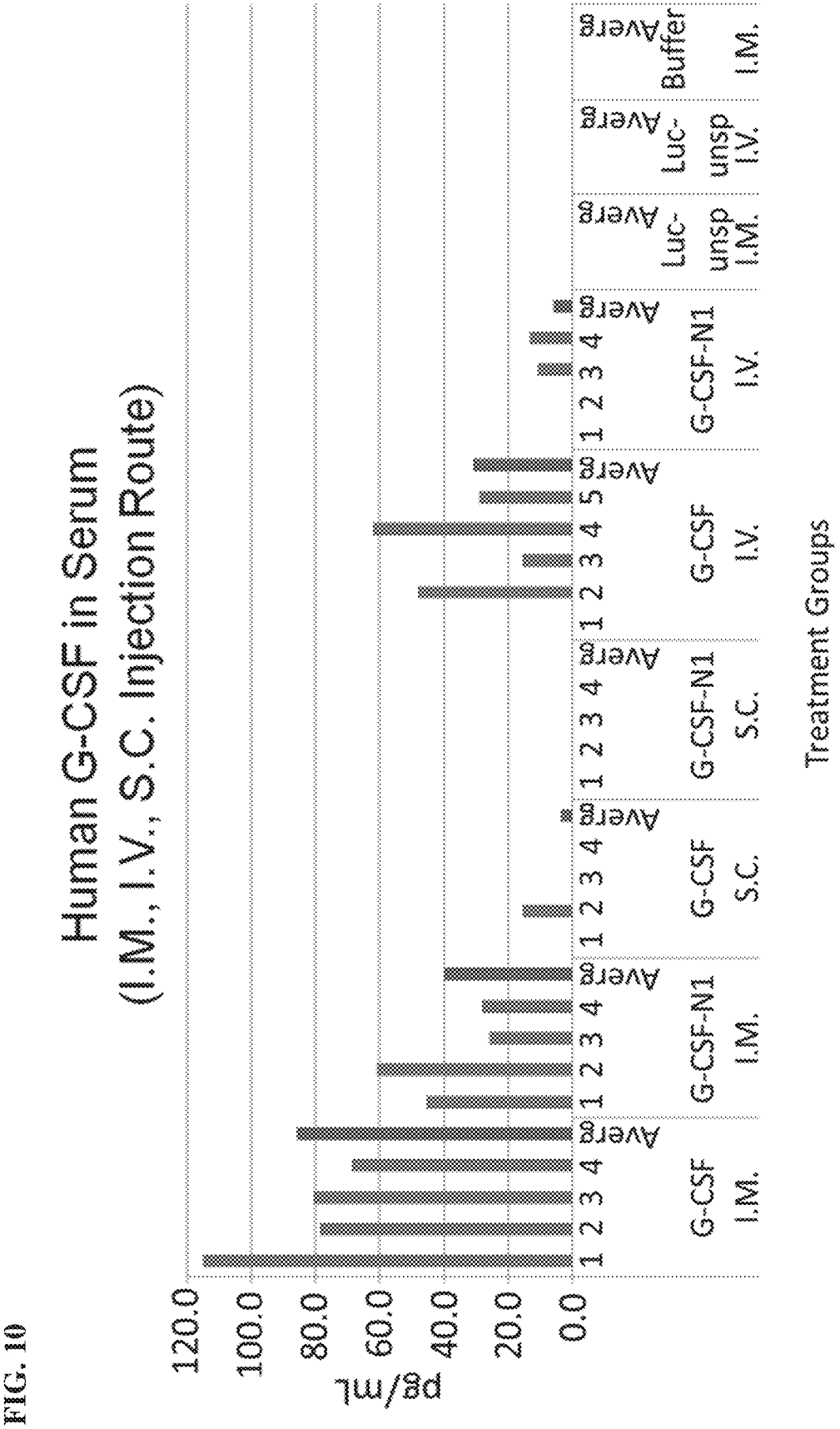

Human G-CSF in Serum
(I.M., I.V., S.C. Injection Route)
pg/mL
120.0
100.0
80.0
60.0
40.0
20.0
0.0
1 2 3 4 Averg
G-CSF I.M.
G-CSF-N1 I.M.
G-CSF S.C.
G-CSF-N1 S.C.
G-CSF I.V.
G-CSF-N1 I.V.
Luc-unsp I.M.
Luc-unsp I.V.
Buffer I.M.
Treatment Groups

FIG. 10

FIG. 11A

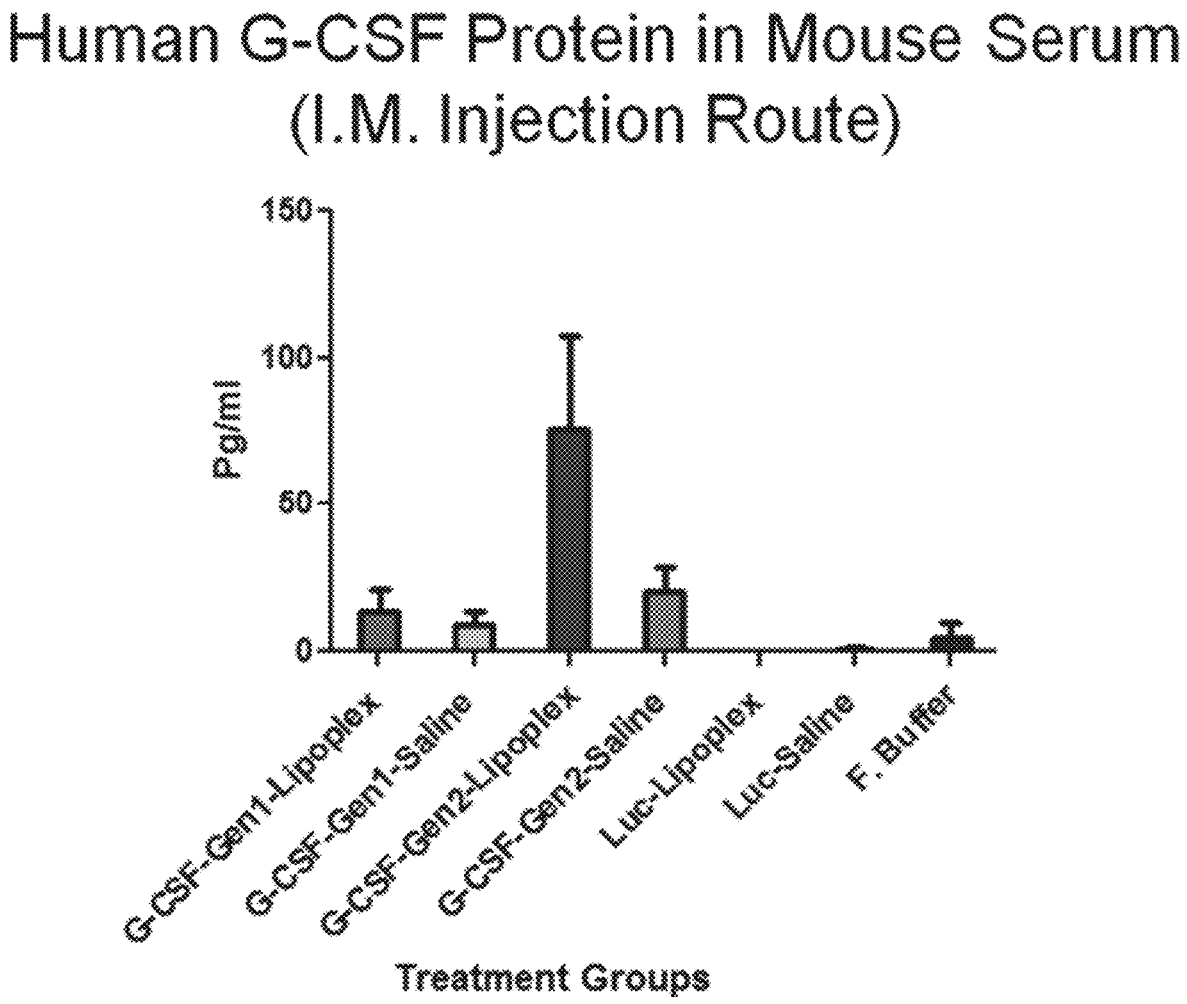

Human G-CSF Protein in Mouse Serum
(I.M. Injection Route)
150
100
50
0
Pg/ml
G-CSF-Gen1-Lipoplex
G-CSF-Gen1-Saline
G-CSF-Gen2-Lipoplex
G-CSF-Gen2-Saline
Luc-Lipoplex
Luc-Saline
F. Buffer
Treatment Groups

FIG. 11B

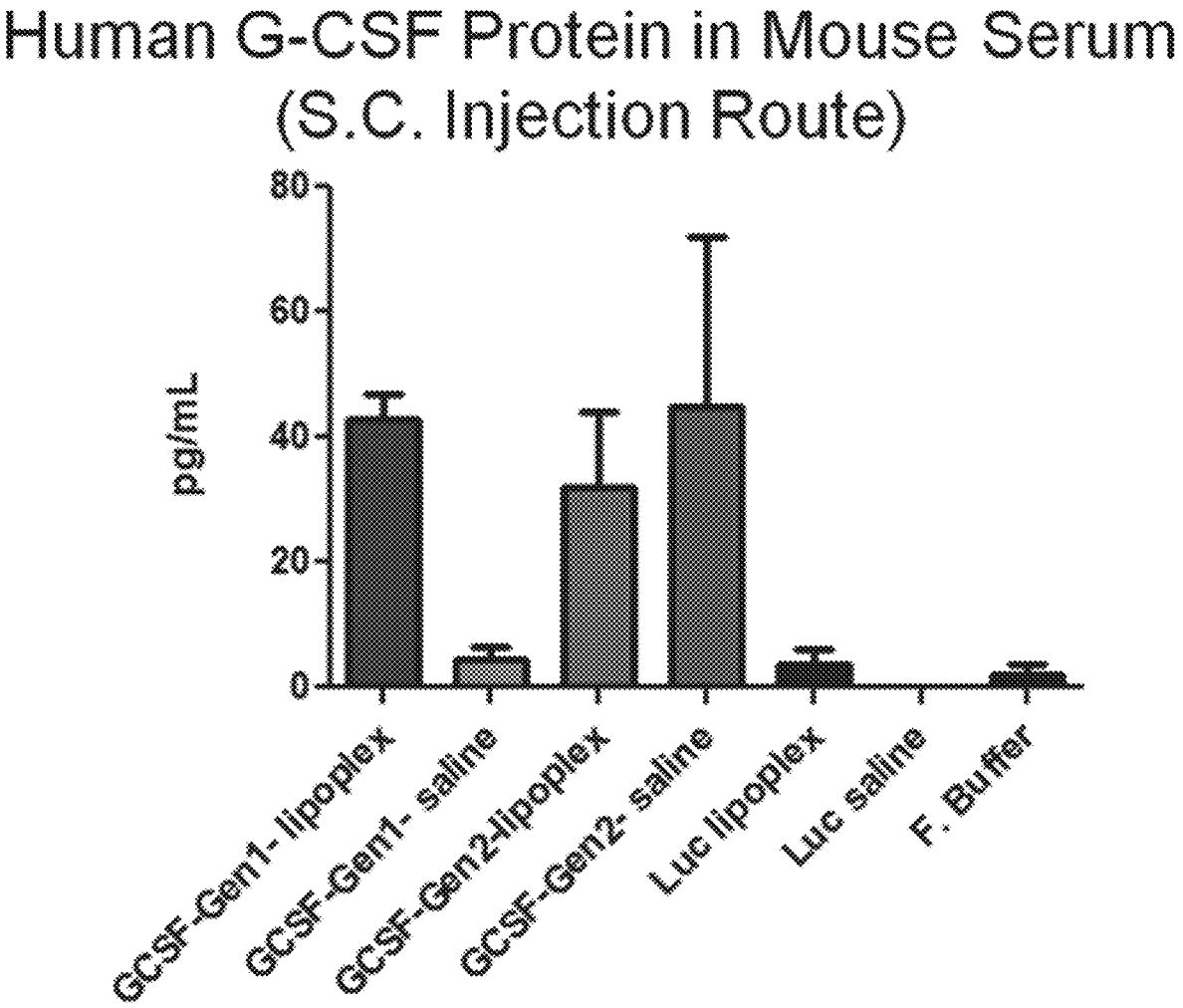
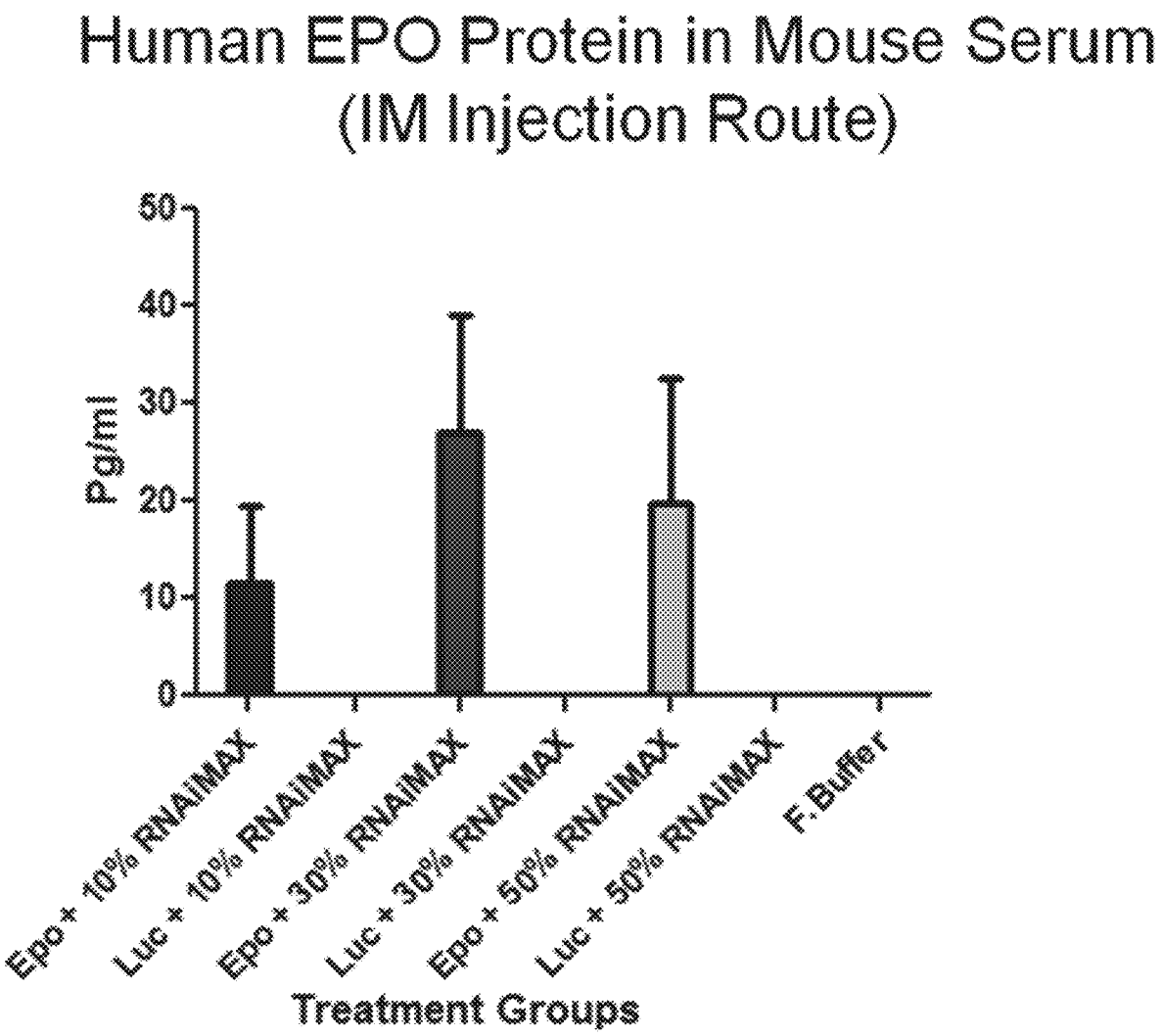

Human G-CSF Protein in Mouse Serum
(S.C. Injection Route)
pg/mL
80
60
40
20
0
GCSF-Gen1- lipoplex
GCSF-Gen1- saline
GCSF-Gen2-lipoplex
GCSF-Gen2- saline
Luc lipoplex
Luc saline
F. Buffer

FIG. 12


Human EPO Protein in Mouse Serum
(IM Injection Route)
Pg/ml
50
40
30
20
10
0
Epo + 10% RNAiMAX
Luc + 10% RNAiMAX
Epo + 30% RNAiMAX
Luc + 30% RNAiMAX
Epo + 50% RNAiMAX
Luc + 50% RNAiMAX
F.Buffer
Treatment Groups

DELIVERY AND FORMULATION OF ENGINEERED NUCLEIC ACIDS

This application is a continuation of U.S. patent application Ser. No. 15/379,284, filed Dec. 14, 2016, entitled Delivery and Formulation of Engineered Nucleic Acids, which is a continuation of U.S. patent application Ser. No. 14/337,513, filed Jul. 22, 2014, entitled Delivery and Formulation of Engineered Nucleic Acids, which is a continuation of U.S. patent application Ser. No. 13/897,362, filed May 18, 2013, entitled Modified Polynucleotides for the Production of Factor IX, which is a continuation of U.S. patent application Ser. No. 13/437,034, filed Apr. 2, 2012, now issued U.S. Pat. No. 8,710,200, entitled Delivery and Formulation of Engineered Nucleic Acids which claims priority to U.S. Provisional Patent Application No. 61/470,451, filed Mar. 31, 2011, entitled Delivery and Formulation of Engineered Nucleic Acids the contents, the contents of each is incorporated by reference in its entirety.

REFERENCE TO SEQUENCE LISTING

The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled M003USSQLST.txt created on May 17, 2013 which is 17,058 bytes in size. The information in electronic format of the sequence listing is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The invention relates to delivery methods. These methods are specifically useful in therapeutic delivery of modified nucleic acids such as modified mRNA (mmRNA).

BACKGROUND OF THE INVENTION

There are multiple problems with prior methodologies of delivering pharmaceutical compositions in order to achieve effective protein expression both for therapeutics and bioprocessing applications. For example, introduced DNA can integrate into host cell genomic DNA at some frequency, resulting in alterations and/or damage to the host cell genomic DNA. Alternatively, the heterologous deoxyribonucleic acid (DNA) introduced into a cell can be inherited by daughter cells (whether or not the heterologous DNA has integrated into the chromosome) or by offspring.

In addition, there are multiple steps which must occur after delivery but before the encoded protein is made which can effect protein expression. Once inside the cell, DNA must be transported into the nucleus where it is transcribed into RNA. The RNA transcribed from DNA must then enter the cytoplasm where it is translated into protein. Not only do the multiple processing steps from administered DNA to protein create lag times before the generation of the functional protein, each step represents an opportunity for error and damage to the cell. Further, it is known to be difficult to obtain DNA expression in cells as frequently DNA enters a cell but is not expressed or not expressed at reasonable rates or concentrations. This can be a particular problem when DNA is introduced into primary cells or modified cell lines.

Assuming the proper management of the foregoing, effective delivery and achievement of therapeutically relevant levels of proteins for a time sufficient to product clinical outcomes remains a significant hurdle.

Consequently, there is a need in the art for the delivery of biological modalities to address pitfalls surrounding the modulation of intracellular translation and processing of nucleic acids encoding polypeptides and therefore optimizing protein expression from the delivered modalities.

The present invention addresses this need by delivering pharmaceutical compositions which can contain modified nucleic acids such as modified mRNA (mmRNA) and may further include formulations to avoid the problems in the art.

SUMMARY OF THE INVENTION

Described herein are compositions and methods for delivery of biological moieties, such as modified nucleic acids, engineered messenger RNA and isolated polynucleotides into cells in order to modulate protein expression.

An isolated polynucleotide may comprise a sequence such as, but not limited to, SEQ ID NO: 4, 7, 8 and 12. The polynucleotide may further comprise a 5'Cap1 structure and a polyA tail of approximately 160 nucleotides in length. Further, the isolated polynucleotide may be formulated in a pharmaceutical composition. A polypeptide of interest may be produced in a cell, tissue or bodily fluid in a subject in need thereof by administering to the subject a pharmaceutical composition comprising a polynucleotide. The polynucleotide may comprise a sequence selected from the group consisting of SEQ ID NO: 4, 7, 8 and 12. The polynucleotide may further comprise a 5'Cap1 structure and a poly-A tail of approximately 160 nucleotides in length.

The pharmaceutical composition may be formulated where the formulation may be selected from, but is not limited to, saline or a lipid formulation. The pharmaceutical composition may be administered by any route of administration such as, but not limited to, intravenous, intramuscular, subcutaneous, and local administration. The lipid formulation may be selected from, but is not limited to, such as, but not limited to, liposomes, lipoplexes, copolymers such as PLGA and lipid nanoparticles

The pharmaceutical composition may be administered at a total dose of about 0.1 mg/kg to about 40 mg/kg. The total dose may be administered by multiple administrations. The administration and/or the multiple administration may occur on a schedule such as, but not limited to, three time a day, twice a day, once a day, every other day, every third day, weekly, biweekly, every three weeks, every four weekly, and monthly.

The modified polypeptide may include a polynucleotide modification such as, but not limited to, a nucleoside modification. The nucleoside modification may include, but is not limited to, pyridin-4-one ribonucleoside, 5-aza-uridine, 2-thio-5-aza-uridine, 2-thiouridine, 4-thio-pseudouridine, 2-thio-pseudouridine, 5-hydroxyuridine, 3-methyluridine, 5-carboxymethyl-uridine, 1-carboxymethyl-pseudouridine, 5-propynyl-uridine, 1-propynyl-pseudouridine, 5-taurinomethyluridine, 1-taurinomethyl-pseudouridine, 5-taurinomethyl-2-thio-uridine, 1-taurinomethyl-4-thio-uridine, 5-methyl-uridine, 1-methyl-pseudouridine, 4-thio-1-methyl-pseudouridine, 2-thio-1-methyl-pseudouridine, 1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-1-deaza-pseudouridine, dihydrouridine, dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-dihydropseudouridine, 2-methoxyuridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, 4-methoxy-2-thio-pseudouridine, 5-aza-cytidine, pseudoisocytidine, 3-methyl-cytidine, N4-acetylcytidine, 5-formylcytidine, N4-methylcytidine, 5-hydroxymethylcytidine, 1-methyl-pseudoisocytidine, pyrrolo-cytidine, pyrrolo-pseudoisocytidine, 2-thio-cytidine, 2-thio-5-methyl-cytidine, 4-thio-pseudoisocytidine, 4-thio-1-methyl-pseudoisocytidine, 4-thio-1-methyl-1-deaza-pseu-

doisocytidine, 1-methyl-1-deaza-pseudoisocytidine, zebularine, 5-aza-zebularine, 5-methyl-zebularine, 5-aza-2-thio-zebularine, 2-thio-zebularine, 2-methoxy-cytidine, 2-methoxy-5-methyl-cytidine, 4-methoxy-pseudoisocytidine, 4-methoxy-1-methyl-pseudoisocytidine, 2-aminopurine, 2, 6-diaminopurine, 7-deaza-adenine, 7-deaza-8-aza-adenine, 7-deaza-2-aminopurine, 7-deaza-8-aza-2-aminopurine, 7-deaza-2,6-diaminopurine, 7-deaza-8-aza-2, 6-diaminopurine, 1-methyladenosine, N6-methyladenosine, N6-isopentenyladenosine, N6-(cis-hydroxyisopentenyl)adenosine, 2-methylthio-N6-(cis-hydroxyisopentenyl) adenosine, N6-glycinylcarbamoyladenosine, N6-threonylcarbamoyladenosine, 2-methylthio-N6-threonyl carbamoyladenosine, N6,N6-dimethyladenosine, 7-methyladenine, 2-methylthio-adenine, and 2-methoxy-adenine, inosine, 1-methyl-inosine, wyosine, wybutosine, 7-deaza-guanosine, 7-deaza-8-aza-guanosine, 6-thio-guanosine, 6-thio-7-deaza-guanosine, 6-thio-7-deaza-8-aza-guanosine, 7-methyl-guanosine, 6-thio-7-methyl-guanosine, 7-methylinosine, 6-methoxy-guanosine, 1-methylguanosine, N2-methyl-guanosine, N2,N2-dimethylguanosine, 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, 1-methyl-6-thio-guanosine, N2-methyl-6-thio-guanosine, and N2,N2-dimethyl-6-thio-guanosine, and combinations thereof.

An increase in the level of a polypeptide of interest can be observed in tissue such as, but not limited to, the liver, spleen, kidney, lung, heart, peri-renal adipose tissue, thymus and muscle and/or in a bodily fluid such as, but not limited to, peripheral blood, serum, plasma, ascites, urine, cerebrospinal fluid (CSF), sputum, saliva, bone marrow, synovial fluid, aqueous humor, amniotic fluid, cerumen, breast milk, broncheoalveolar lavage fluid, semen, prostatic fluid, cowper's fluid or pre-ejaculatory fluid, sweat, fecal matter, hair, tears, cyst fluid, pleural and peritoneal fluid, pericardial fluid, lymph, chyme, chyle, bile, interstitial fluid, menses, pus, sebum, vomit, vaginal secretions, mucosal secretion, stool water, pancreatic juice, lavage fluids from sinus cavities, bronchopulmonary aspirates, blastocyl cavity fluid, and umbilical cord blood. The increased level can be observed in the tissue and/or bodily fluid of the subject within 2, 8 and/or 24 hours after administration. Further, the increased level can be determined from the level of a modified polypeptide in an exosome.

The details of various embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and the drawings, and from the claims.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** illustrates lipid structures in the prior art useful in the present invention. Shown are the structures for 98N12-5 (TETA5-LAP), DLin-DMA, DLin-K-DMA (2,2-Dilinoleyl-4-dimethylaminomethyl-[1,3]-dioxolane), DLin-KC2-DMA, DLin-MC3-DMA and C12-200.

FIG. **2** is a representative plasmid useful in the IVT reactions taught herein. The plasmid contains Insert 64818, designed by the instant inventors.

FIGS. **3**A and **3**B are histograms showing in vitro screening results for nanoparticle formulations of DLin-KC2-DMA and 98N12-15 (before and after purification) that contain mCherry mmRNA. FIG. **3**A shows the screening results in HEK293 cells and FIG. **3**B shows the screening results in HepG2 cells.

FIGS. **4**A and **4**B are histograms showing in vitro screening results for mean fluorescence intensity for nanoparticle formulations of DLin-KC2-DMA and 98N12-15 (before and after purification) that contain mCherry mmRNA. FIG. **4**A shows the screening results in HEK293 cells and FIG. **4**B shows the screening results in HepG2 cells.

FIGS. **5**A, **5**B, and **5**C are histograms showing in vitro screening results for nanoparticle formulations of DLin-KC2-DMA and 98N12-15 before and after purification. FIG. **5**A shows the screening results of 98N15-2 in HEK293 cells, and FIGS. **5**B and **5**C shows the screening results of DLin-KC2-DMA in HEK293 cells.

FIGS. **6**A, **6**B, **6**C, and **6**D are histograms showing in vitro screening results for nanoparticle formulations of DLin-DMA, DLin-K-DMA, DLin-KC2-DMA, 98N12-5, C12-200 and DLin-MC3-DMA that contain mCherry mmRNA. FIG. **6**A shows the mean fluorescence intensity of mCherry in HEK293 cells containing 60 ng of modified mCherry mRNA per well. FIGS. **6**B and **6**C show the mean fluorescence intensity of mCherry in HEK293 cells which contained nanoparticles formulations having a concentration of 62.5 ng/well of modified mCherry mRNA. FIGS. **6**D and **6**E show the mean fluorescence intensity of mCherry in HepG2 cells which contained nanoparticle formulations having a concentration of 62.5 ng/well of modified mCherry mRNA.

FIGS. **7**A and **7**B are histograms showing in vivo screening results of human erythropoietin in serum after the administration of modified human erythropoietin mmRNA or luciferase mmRNA in mice. FIG. **7**A shows the concentration in pg/ml of human erythropoietin after intramuscular administration. FIG. **7**B shows the concentration in pg/ml of human erythropoietin after subcutaneous administration.

FIGS. **8**A, **8**B, **8**C, and **8**D are histograms of in vivo screening results from biophotoic imaging. FIG. **8**A is a histogram of bioluminescence (photon/sec) from the intramuscular injection of 5 ug in the left hind leg. FIG. **8**B is a histogram of bioluminescence from the intramuscular injection of 50 ug in the right hind leg. FIG. **8**C is a histogram showing in vivo screening results from biophotoic imaging after a subcutaneous injection of 50 ug. FIG. **8**D is a histogram showing in vivo screening results from biophotoic imaging after a administration of 50 ug intravenously.

FIG. **9** is a histogram showing in vivo screening results for modified human G-CSF mmRNA administered intramuscularly, subcutaneously or intravenously in mice.

FIG. **10** is a histogram showing in vivo screening results for modified G-CSF administered intramuscularly, subcutaneously or intravenously.

FIGS. **11**A and **11**B are histograms showing in vivo screening results of modified human G-CSF mmRNA administered intramuscularly or subcutaneously in mice. FIG. **11**A shows the concentration in pg/ml of human G-CSF in serum after the administration of modified G-CSF intramuscularly. FIG. **11**B shows the concentration in pg/ml of human G-CSF in serum after the administration of modified G-CSF subcutaneously.

FIG. **12** is a histogram showing in vivo screening results of human erythropoietin in serum after the administration of modified human erythropoietin mmRNA or luciferase mmRNA administered intramuscularly in mice.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as those commonly understood to one of ordinary skill in the art to which this invention pertains.

DETAILED DESCRIPTION

Described herein are compositions and methods for the delivery of modified mRNA molecules in order to modulate protein expression.

As described herein and as in copending, co-owned applications International Application PCT/US2011/046861 filed Aug. 5, 2011 and PCT/US2011/054636 filed Oct. 3, 2011, the contents of which are incorporated by reference herein in their entirety, these modified nucleic acid molecules are capable of reducing the innate immune activity of a population of cells into which they are introduced, thus increasing the efficiency of protein production in that cell population.

Modified mRNAs (mmRNAs)

This invention provides nucleic acids, including RNAs, specifically mRNAs, that encode at least one polypeptide and contain one or more modified nucleosides (termed "modified nucleic acids" or "modified nucleic acid molecules" or "engineered nucleic acids"), which have useful properties including the lack of a substantial induction of the innate immune response of a cell into which the mRNA is introduced. Because these mmRNAs enhance the efficiency of protein production, intracellular retention of nucleic acids, and viability of contacted cells, as well as possess reduced immunogenicity, these nucleic acids having these properties are termed "enhanced" nucleic acids or modified RNAs herein.

The term "nucleic acid," in its broadest sense, includes any compound and/or substance that comprise a polymer of nucleotides linked via a phosphodiester bond. These polymers are often referred to as oligonucleotides.

Exemplary nucleic acids include ribonucleic acids (RNAs), deoxyribonucleic acids (DNAs), threose nucleic acids (TNAs), glycol nucleic acids (GNAs), peptide nucleic acids (PNAs), locked nucleic acids (LNAs) or hybrids thereof. They may also include RNAi-inducing agents, RNAi agents, siRNAs, shRNAs, miRNAs, antisense RNAs, ribozymes, catalytic DNA, tRNA, RNAs that induce triple helix formation, aptamers, vectors, etc.

In preferred embodiments, the nucleic acid is one or more modified messenger RNAs (mmRNAs). As described herein, in some embodiments the mmRNAs of the invention do not substantially induce an innate immune response of a cell into which the mRNA is introduced.

The mmRNA of the present invention may encode one or more polypeptides. Generally the polypeptides of interest are those which are naturally occurring in the mammalian genome.

According to the present invention, the shortest length of a modified mRNA, herein "mmRNA," of the present disclosure can be the length of an mRNA sequence that may be sufficient to encode for a dipeptide. In another embodiment, the length of the mRNA sequence may be sufficient to encode for a tripeptide. In another embodiment, the length of an mRNA sequence may be sufficient to encode for a tetrapeptide. In another embodiment, the length of an mRNA sequence may be sufficient to encode for a pentapeptide. In another embodiment, the length of an mRNA sequence may be sufficient to encode for a hexapeptide. In another embodiment, the length of an mRNA sequence may be sufficient to encode for a heptapeptide. In another embodiment, the length of an mRNA sequence may be sufficient to encode for an octapeptide. In another embodiment, the length of an mRNA sequence may be sufficient to encode for a nonapeptide. In another embodiment, the length of an mRNA sequence may be sufficient to encode for a decapeptide.

Generally, the length of a modified mRNA of the present invention is greater than about 30 nucleotides in length (e.g., at least or greater than about 35, 40, 45, 50, 55, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, 1,000, 1,100, 1,200, 1,300, 1,400, 1,500, 1,600, 1,700, 1,800, 1,900, 2,000, 2,500, and 3,000, 4,000, 5,000, 6,000, 7,000, 8,000, 9,000, 10,000, 20,000, 30,000, 40,000, 50,000, 60,000, 70,000, 80,000, 90,000 or up to and including 100,000 nucleotides).

In some embodiments, the modified mRNA of the present invention includes from about 30 to about 100,000 nucleotides (e.g., from 30 to 50, from 30 to 100, from 30 to 250, from 30 to 500, from 30 to 1,000, from 30 to 1,500, from 30 to 3,000, from 30 to 5,000, from 30 to 7,000, from 30 to 10,000, from 30 to 25,000, from 30 to 50,000, from 30 to 70,000, from 100 to 250, from 100 to 500, from 100 to 1,000, from 100 to 1,500, from 100 to 3,000, from 100 to 5,000, from 100 to 7,000, from 100 to 10,000, from 100 to 25,000, from 100 to 50,000, from 100 to 70,000, from 100 to 100,000, from 500 to 1,000, from 500 to 1,500, from 500 to 2,000, from 500 to 3,000, from 500 to 5,000, from 500 to 7,000, from 500 to 10,000, from 500 to 25,000, from 500 to 50,000, from 500 to 70,000, from 500 to 100,000, from 1,000 to 1,500, from 1,000 to 2,000, from 1,000 to 3,000, from 1,000 to 5,000, from 1,000 to 7,000, from 1,000 to 10,000, from 1,000 to 25,000, from 1,000 to 50,000, from 1,000 to 70,000, from 1,000 to 100,000, from 1,500 to 3,000, from 1,500 to 5,000, from 1,500 to 7,000, from 1,500 to 10,000, from 1,500 to 25,000, from 1,500 to 50,000, from 1,500 to 70,000, from 1,500 to 100,000, from 2,000 to 3,000, from 2,000 to 5,000, from 2,000 to 7,000, from 2,000 to 10,000, from 2,000 to 25,000, from 2,000 to 50,000, from 2,000 to 70,000, and from 2,000 to 100,000).

Polypeptide Variants

The mmRNA of the present invention may encode variant polypeptides, which have a certain identity with a reference polypeptide sequence, for example a wild type mRNA. The term "identity" as known in the art, refers to a relationship between the sequences of two or more peptides, as determined by comparing the sequences. In the art, "identity" also means the degree of sequence relatedness between peptides, as determined by the number of matches between strings of two or more amino acid residues. "Identity" measures the percent of identical matches between the smaller of two or more sequences with gap alignments (if any) addressed by a particular mathematical model or computer program (i.e., "algorithms"). Identity of related peptides can be readily calculated by known methods. Such methods include, but are not limited to, those described in Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Computer Analysis of Sequence Data, Part 1, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M. Stockton Press, New York, 1991; and Carillo et al., SIAM J. Applied Math. 48, 1073 (1988).

In some embodiments, the polypeptide variant has the same or a similar activity as the reference polypeptide. Alternatively, the variant has an altered activity (e.g., increased or decreased) relative to a reference polypeptide. Generally, variants of a particular polynucleotide or polypeptide of the invention will have at least about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to that particular reference polynucleotide or polypeptide as determined by sequence alignment programs and parameters described herein and known to those skilled in the art.

As recognized by those skilled in the art, protein fragments, functional protein domains, and homologous proteins are also considered to be within the scope of this invention. For example, provided herein is any protein fragment of a reference protein (meaning a polypeptide sequence at least one amino acid residue shorter than a reference polypeptide sequence but otherwise identical) 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or greater than 100 amino acids in length In another example, any protein that includes a stretch of about 20, about 30, about 40, about 50, or about 100 amino acids which are about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, or about 100% identical to any of the sequences described herein can be utilized in accordance with the invention. In certain embodiments, a protein sequence to be utilized in accordance with the invention includes 2, 3, 4, 5, 6, 7, 8, 9, 10, or more mutations as shown in any of the sequences provided or referenced herein.

Targeting Moieties

In embodiments of the invention, mmRNAs are provided to express a protein-binding partner or a receptor on the surface of the cell, which functions to target the cell to a specific tissue space or to interact with a specific moiety, either in vivo or in vitro. Suitable protein-binding partners include antibodies and functional fragments thereof, scaffold proteins, or peptides.

Cell Penetrating Peptides

The mmRNAs disclosed herein may encode a cell-penetrating polypeptide. As used herein, "cell-penetrating polypeptide" refers to a polypeptide which may facilitate the cellular uptake of molecules. It is known in the art that "CPP" refers to cell-penetration polypeptides and cell-penetrating peptides. When used herein, it will be clarified as to which of either cell-penetrating polypeptides or cell-penetrating peptides the abbreviation CPP refers to.

A cell-penetrating polypeptide of the present invention may contain one or more detectable labels. The polypeptides may be partially labeled or completely labeled throughout. The mmRNA may encode the detectable label completely, partially or not at all. The cell-penetrating peptide may also include a signal sequence. As used herein, a "signal sequence" refers to a sequence of amino acid residues bound at the amino terminus of a nascent protein during protein translation. The signal sequence may be used to signal the secretion of the cell-penetrating polypeptide.

Fusion Proteins

The modified nucleic acids and mmRNA may encode a fusion protein. The fusion protein may be created by operably linking a charged protein to a therapeutic protein. As used herein, "operably linked" refers to the therapeutic protein and the charged protein being connected in such a way to permit the expression of the complex when introduced into the cell. As used herein, "charged protein" refers to a protein that carries a positive, negative or overall neutral electrical charge. Preferably, the therapeutic protein may be covalently linked to the charged protein in the formation of the fusion protein. The ratio of surface charge to total or surface amino acids may be approximately 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8 or 0.9.

Synthesis of Modified mRNAs

Nucleic acids for use in accordance with the invention may be prepared according to any available technique including, but not limited to chemical synthesis, enzymatic synthesis, which is generally termed in vitro transcription, enzymatic or chemical cleavage of a longer precursor, etc. Methods of synthesizing RNAs are known in the art (see, e.g., Gait, M. J. (ed.) *Oligonucleotide synthesis: a practical approach*, Oxford [Oxfordshire], Washington, D.C.: IRL Press, 1984; and Herdewijn, P. (ed.) *Oligonucleotide synthesis: methods and applications*, Methods in Molecular Biology, v. 288 (Clifton, N.J.) Totowa, N.J.: Humana Press, 2005; both of which are incorporated herein by reference).

The modified nucleosides and nucleotides used in the synthesis of modified RNAs disclosed herein can be prepared from readily available starting materials using the following general methods and procedures. It is understood that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given; other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

The manufacturing process herein can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^{1}H or ^{13}C) infrared spectroscopy, spectrophotometry (e.g., UV-visible), or mass spectrometry, or by chromatography such as high performance liquid chromatography (HPLC) or thin layer chromatography.

Modification of mRNAs

Provided are mmRNAs containing a translatable region and one, two, or more than two different modifications.

In some embodiments, the chemical modifications can be located on the nucleobase of the nucleotide.

In some embodiments, the chemical modifications can be located on the sugar moiety of the nucleotide.

In some embodiments, the chemical modifications can be located on the phosphate backbone of the nucleotide.

Preparation of modified nucleosides and nucleotides used in the manufacture or synthesis of modified RNAs of the present invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups can be readily determined by one skilled in the art.

The chemistry of protecting groups can be found, for example, in Greene, et al., *Protective Groups in Organic Synthesis,* 2d. Ed., Wiley & Sons, 1991, which is incorporated herein by reference in its entirety.

Modified nucleosides and nucleotides can be prepared according to the synthetic methods described in Ogata et al. *Journal of Organic Chemistry* 74:2585-2588, 2009; Purmal et al. *Nucleic Acids Research* 22(1): 72-78, 1994; Fukuhara et al. *Biochemistry* 1(4): 563-568, 1962; and Xu et al. *Tetrahedron* 48(9): 1729-1740, 1992, each of which are incorporated by reference in their entirety.

Modified mRNAs need not be uniformly modified along the entire length of the molecule. Different nucleotide modifications and/or backbone structures may exist at various positions in the nucleic acid. One of ordinary skill in the art will appreciate that the nucleotide analogs or other modification(s) may be located at any position(s) of a nucleic acid such that the function of the nucleic acid is not substantially decreased. A modification may also be a 5' or 3' terminal modification. The nucleic acids may contain at a minimum one and at maximum 100% modified nucleotides, or any intervening percentage, such as at least 50% modified nucleotides, at least 80% modified nucleotides, or at least 90% modified nucleotides.

For example, the mmRNAs may contain a modified pyrimidine such as uracil or cytosine. In some embodiments, at least 5%, at least 10%, at least 25%, at least 50%, at least 80%, at least 90% or 100% of the uracil in the nucleic acid

may be replaced with a modified uracil. The modified uracil can be replaced by a compound having a single unique structure, or can be replaced by a plurality of compounds having different structures (e.g., 2, 3, 4 or more unique structures). In some embodiments, at least 5%, at least 10%, at least 25%, at least 50%, at least 80%, at least 90% or 100% of the cytosine in the nucleic acid may be replaced with a modified cytosine. The modified cytosine can be replaced by a compound having a single unique structure, or can be replaced by a plurality of compounds having different structures (e.g., 2, 3, 4 or more unique structures).

In some embodiments, modified nucleosides include pyridin-4-one ribonucleoside, 5-aza-uridine, 2-thio-5-aza-uridine, 2-thiouridine, 4-thio-pseudouridine, 2-thio-pseudouridine, 5-hydroxyuridine, 3-methyluridine, 5-carboxymethyl-uridine, 1-carboxymethyl-pseudouridine, 5-propynyl-uridine, 1-propynyl-pseudouridine, 5-taurinomethyluridine, 1-taurinomethyl-pseudouridine, 5-taurinomethyl-2-thio-uridine, 1-taurinomethyl-4-thio-uridine, 5-methyl-uridine, 1-methyl-pseudouridine, 4-thio-1-methyl-pseudouridine, 2-thio-1-methyl-pseudouridine, 1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-1-deaza-pseudouridine, dihydrouridine, dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-dihydropseudouridine, 2-methoxyuridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, and 4-methoxy-2-thio-pseudouridine. In some embodiments, modified nucleosides include 5-aza-cytidine, pseudoisocytidine, 3-methyl-cytidine, N4-acetylcytidine, 5-formylcytidine, N4-methylcytidine, 5-hydroxymethylcytidine, 1-methyl-pseudoisocytidine, pyrrolo-cytidine, pyrrolo-pseudoisocytidine, 2-thio-cytidine, 2-thio-5-methyl-cytidine, 4-thio-pseudoisocytidine, 4-thio-1-methyl-pseudoisocytidine, 4-thio-1-methyl-1-deaza-pseudoisocytidine, 1-methyl-1-deaza-pseudoisocytidine, zebularine, 5-aza-zebularine, 5-methyl-zebularine, 5-aza-2-thio-zebularine, 2-thio-zebularine, 2-methoxy-cytidine, 2-methoxy-5-methyl-cytidine, 4-methoxy-pseudoisocytidine, and 4-methoxy-1-methyl-pseudoisocytidine.

In other embodiments, modified nucleosides include 2-aminopurine, 2, 6-diaminopurine, 7-deaza-adenine, 7-deaza-8-aza-adenine, 7-deaza-2-aminopurine, 7-deaza-8-aza-2-aminopurine, 7-deaza-2,6-diaminopurine, 7-deaza-8-aza-2,6-diaminopurine, 1-methyladenosine, N6-methyladenosine, N6-isopentenyladenosine, N6-(cis-hydroxyisopentenyl)adenosine, 2-methylthio-N6-(cis-hydroxyisopentenyl) adenosine, N6-glycinylcarbamoyladenosine, N6-threonylcarbamoyladenosine, 2-methylthio-N6-threonyl carbamoyladenosine, N6,N6-dimethyladenosine, 7-methyl-adenine, 2-methylthio-adenine, and 2-methoxy-adenine.

In other embodiments, modified nucleosides include inosine, 1-methyl-inosine, wyosine, wybutosine, 7-deaza-guanosine, 7-deaza-8-aza-guanosine, 6-thio-guanosine, 6-thio-7-deaza-guanosine, 6-thio-7-deaza-8-aza-guanosine, 7-methyl-guanosine, 6-thio-7-methyl-guanosine, 7-methyl-inosine, 6-methoxy-guanosine, 1-methylguanosine, N2-methylguanosine, N2,N2-dimethylguanosine, 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, 1-methyl-6-thio-guanosine, N2-methyl-6-thio-guanosine, and N2,N2-dimethyl-6-thio-guanosine.

In some embodiments, the nucleotide can be modified on the major groove face and can include replacing hydrogen on C-5 of uracil with a methyl group or a halo group.

In specific embodiments, a modified nucleoside is 5'-O-(1-Thiophosphate)-Adenosine, 5'-O-(1-Thiophosphate)-Cytidine, 5'-O-(1-Thiophosphate)-Guanosine, 5'-O-(1-Thiophosphate)-Uridine or 5'-O-(1-Thiophosphate)-Pseudouridine.

Further examples of modified nucleotides and modified nucleotide combinations are provided below in Table 1.

TABLE 1

Modified Nucleotides	Modified Nucleotide Combinations
6-aza-cytidine	α-thio-cytidine/5-iodo-uridine
2-thio-cytidine	α-thio-cytidine/N1-methyl-pseudo-uridine
α-thio-cytidine	α-thio-cytidine/α-thio-uridine
Pseudo-iso-cytidine	α-thio-cytidine/5-methyl-uridine
5-aminoallyl-uridine	α-thio-cytidine/pseudo-uridine
5-iodo-uridine	Pseudo-iso-cytidine/5-iodo-uridine
N1-methyl-pseudouridine	Pseudo-iso-cytidine/N1-methyl-pseudo-uridine
5,6-dihydrouridine	Pseudo-iso-cytidine/α-thio-uridine
α-thio-uridine	Pseudo-iso-cytidine/5-methyl-uridine
4-thio-uridine	Pseudo-iso-cytidine/Pseudo-uridine
6-aza-uridine	Pyrrolo-cytidine
5-hydroxy-uridine	Pyrrolo-cytidine/5-iodo-uridine
Deoxy-thymidine	Pyrrolo-cytidine/N1-methyl-pseudo-uridine
Pseudo-uridine	Pyrrolo-cytidine/α-thio-uridine
Inosine	Pyrrolo-cytidine/5-methyl-uridine
α-thio-guanosine	Pyrrolo-cytidine/Pseudo-uridine
8-oxo-guanosine	5-methyl-cytidine/5-iodo-uridine
O6-methyl-guanosine	5-methyl-cytidine/N1-methyl-pseudo-uridine
7-deaza-guanosine	5-methyl-cytidine/α-thio-uridine
No modification	5-methyl-cytidine/5-methyl-uridine
N1-methyl-adenosine	5-methyl-cytidine/Pseudo-uridine
2-amino-6-Chloro-purine	5-methyl-cytidine
N6-methyl-2-amino-purine	25% Pseudo-iso-cytidine
6-Chloro-purine	25% N1-methyl-pseudo-uridine
N6-methyl-adenosine	25% N1-Methyl-pseudo-uridine/75%-pseudo-uridine
α-thio-adenosine	5-methyl-uridine
8-azido-adenosine	5-iodo-cytidine
7-deaza-adenosine	

In some embodiments, at least 25% of the cytosines are replaced by a compound of Formula I-a (e.g., at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100%).

In some embodiments, at least 25% of the uracils are replaced by a compound of Formula I-a (e.g., at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100%).

In some embodiments, at least 25% of the cytosines and 25% of the uracils are replaced by a compound of Formula I-a (e.g., at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100%).

Other components of nucleic acid are optional, and are beneficial in some embodiments. For example, a 5' untranslated region (UTR) and/or a 3'UTR are provided, wherein either or both may independently contain one or more different nucleoside modifications. In such embodiments, nucleoside modifications may also be present in the translatable region. Also provided are nucleic acids containing a Kozak sequence.

Linkers and Payloads

The nucleobase of the nucleotide, which may be incorporated into a mmRNA, can be covalently linked at any chemically appropriate position to a payload, e.g. detectable agent or therapeutic agent. For example, the nucleobase can be deaza-adenosine or deaza-guanosine and the linker can be attached at the C-7 or C-8 positions of the deaza-adenosine or deaza-guanosine. In other embodiments, the nucleobase can be cytosine or uracil and the linker can be attached to the N-3 or C-5 positions of cytosine or uracil.

Linker

The term "linker" as used herein refers to a group of atoms, e.g., 10-1,000 atoms, and can be comprised of the atoms or groups such as, but not limited to, carbon, amino, alkylamino, oxygen, sulfur, sulfoxide, sulfonyl, carbonyl, and imine. The linker can be attached to a modified nucleoside or nucleotide on the nucleobase or sugar moiety at a first end, and to a payload, e.g., detectable or therapeutic agent, at a second end. The linker may be of sufficient length as to not interfere with incorporation into a nucleic acid sequence.

Examples of chemical groups that can be incorporated into the linker include, but are not limited to, an alkyl, an alkene, an alkyne, an amido, an ether, a thioether or an ester group. The linker chain can also comprise part of a saturated, unsaturated or aromatic ring, including polycyclic and heteroaromatic rings wherein the heteroaromatic ring may be an aryl group containing one to four heteroatoms, N, O or S. Specific examples of linkers include, but are not limited to, unsaturated alkanes, polyethylene glycols, and dextran polymers.

For example, the linker can include, but is not limited to, ethylene or propylene glycol monomeric units, e.g., diethylene glycol, dipropylene glycol, triethylene glycol, tripropylene glycol, tetraethylene glycol, or tetraethylene glycol. In some embodiments, the linker can include, but is not limited to, a divalent alkyl, alkenyl, and/or alkynyl moiety. The linker can include an ester, amide, or ether moiety.

Other examples include, but are not limited to, cleavable moieties within the linker, such as, for example, a disulfide bond (—S—S—) or an azo bond (—N═N—), which can be cleaved using a reducing agent or photolysis. When a cleavable bond which has been incorporated into the linker and attached to a modified nucleotide, is cleaved, a short "scar" or chemical modification on the nucleotide may result. For example, after cleaving, the resulting scar on a nucleotide base, which formed part of the modified nucleotide, and is incorporated into a polynucleotide strand, is unreactive and does not need to be chemically neutralized. This increases the ease with which a subsequent nucleotide can be incorporated during sequencing of a nucleic acid polymer template. For example, conditions include the use of tris(2-carboxyethyl)phosphine (TCEP), dithiothreitol (DTT) and/or other reducing agents for cleavage of a disulfide bond. A selectively severable bond that includes an amido bond can be cleaved for example by the use of TCEP or other reducing agents, and/or photolysis. A selectively severable bond that includes an ester bond can be cleaved for example by acidic or basic hydrolysis.

Detectable Agents

The mmRNAs of the present invention may also be linked or conjugated to one or more detectable agents. Examples of detectable substances include, but are not limited to, various organic small molecules, inorganic compounds, nanoparticles, enzymes or enzyme substrates, fluorescent materials, luminescent materials, bioluminescent materials, chemiluminescent materials, radioactive materials, and contrast agents.

Labels, other than those described herein, are contemplated by the present disclosure, including, but not limited to, other optically-detectable labels. Labels can be attached to the modified nucleotide of the present disclosure at any position using standard chemistries such that the label can be removed from the incorporated base upon cleavage of the cleavable linker.

Terminal Architecture Modifications: 5'-Capping

Endogenous eukaryotic cellular messenger RNA (mRNA) molecules contain a 5'-cap structure on the 5'-end of a mature mRNA molecule. The 5'-cap contains a 5'-5'-triphosphate linkage between the 5'-most nucleotide and guanine nucleotide. The conjugated guanine nucleotide is methylated at the N7 position. Additional modifications include methylation of the ultimate and penultimate most 5'-nucleotides on the 2'-hydroxyl group. The 5'-cap structure is responsible for binding the mRNA Cap Binding Protein (CBP), which is responsibility for mRNA stability in the cell and translation competency.

Multiple distinct 5'-cap structures can be used to generate the 5'-cap of a synthetic mRNA molecule. Many chemical cap analogs are used to co-transcriptionally cap a synthetic mRNA molecule. For example, the Anti-Reverse Cap Analog (ARCA) cap contains a 5'-5'-triphosphate guanine-guanine linkage where one guanine contains an N7 methyl group as well as a 3'-O-methyl group. While chemical cap analogs allow for the concomitant capping of an RNA molecule, up 20% of transcripts remain uncapped and the synthetic cap analog is not identical to an endogenous 5'-cap structure of an authentic cellular mRNA. This may lead to reduced translationally-competency and reduced cellular stability.

Synthetic mRNA molecules may also be capped post-transcriptionally using enzymes responsible for generating a more authentic 5'-cap structure. As used herein the phrase "more authentic" refers to a feature that closely mirrors or mimics, either structurally or functionally an endogenous or wild type feature. More authentic 5'-cap structures of the present invention are those which, among other things, have enhanced binding of cap binding proteins, increased half life, reduced susceptibility to 5' endonucleases and/or reduced 5'decapping. For example, recombinant Vaccinia Virus Capping Enzyme and recombinant 2'-O-methyltransferase enzyme can create a canonical 5'-5'-triphosphate linkage between the 5'-most nucleotide of an mRNA and a guanine nucleotide where the guanine contains an N7 methylation and the ultimate 5'-nucleotide contains a 2'-O-methyl generating the Cap1 structure. This results in a cap with higher translational-competency and cellular stability and reduced activation of cellular pro-inflammatory cytokines. Because the synthetic mRNA is capped post-transcriptionally, nearly 100% of the mRNA molecules are capped in contrast to ~80% of synthetic mRNAs containing a chemical cap analog.

Terminal Architecture Modifications: Poly-A Tails

During RNA processing, a long chain of adenine nucleotides (poly-A tail) is normally added to a messenger RNA (mRNA) molecules to increase the stability of the molecule. Immediately after transcription, the 3' end of the transcript is cleaved to free a 3' hydroxyl. Then poly-A polymerase adds a chain of adenine nucleotides to the RNA. The process, called polyadenylation, adds a poly-A tail that is between 100 and 250 residues long.

It has been discovered that unique poly-A tail lengths provide certain advantages to the modified RNAs of the present invention.

Generally, the length of a poly-A tail of the present invention is greater than 30 nucleotides in length. In another embodiment, the poly-A tail is greater than 35 nucleotides in length. In another embodiment, the length is at least 40 nucleotides. In another embodiment, the length is at least 45 nucleotides. In another embodiment, the length is at least 55 nucleotides. In another embodiment, the length is at least 60 nucleotides. In another embodiment, the length is at least 60 nucleotides. In another embodiment, the length is at least 80 nucleotides. In another embodiment, the length is at least 90 nucleotides. In another embodiment, the length is at least 100 nucleotides. In another embodiment, the length is at least 120 nucleotides. In another embodiment, the length is at least 140 nucleotides. In another embodiment, the length is at least 160 nucleotides. In another embodiment, the length is at least 180 nucleotides. In another embodiment, the length is at least 200 nucleotides. In another embodiment, the length is at least 250 nucleotides. In another embodiment, the length is at least 300 nucleotides. In another embodiment, the length is at least 350 nucleotides. In another embodiment, the length is at least 400 nucleotides. In another embodiment, the length is at least 450 nucleotides. In another embodiment, the length is at least 500 nucleotides. In another embodiment, the length is at least 600 nucleotides. In another embodiment, the length is at least 700 nucleotides. In another embodiment, the length is at least 800 nucleotides. In another embodiment, the length is at least 900 nucleotides. In another embodiment, the length is at least 1000 nucleotides.

In one embodiment, the poly-A tail is designed relative to the length of the overall modified RNA molecule. This design may be based on the length of the coding region of the modified RNA, the length of a particular feature or region of the modified RNA (such as the mRNA), or based on the length of the ultimate product expressed from the modified RNA. In this context the poly-A tail may be 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100% greater in length than the modified RNA or feature thereof. The poly-A tail may also be designed as a fraction of the modified RNA to which it belongs. In this context, the poly-A tail may be 10, 20, 30, 40, 50, 60, 70, 80, or 90% or more of the total length of the construct or the total length of the construct minus the poly-A tail.

Use of Modified mRNAs

The mmRNAs of the present invention may find uses in many areas of research, discovery, therapeutics, diagnostics and in kits and devices.

Therapeutics

The mmRNAs (modified RNAs) and the proteins translated from the mmRNAs described herein can be used as therapeutic agents. For example, an mmRNA described herein can be administered to a subject, wherein the mmRNA is translated in vivo to produce a therapeutic polypeptide in the subject. Provided are compositions, methods, kits, and reagents for treatment or prevention of disease or conditions in humans and other mammals. The active therapeutic agents of the invention include mmRNAs, cells containing mmRNAs or polypeptides translated from the mmRNAs, polypeptides translated from mmRNAs.

Provided herein are methods of inducing translation of a recombinant polypeptide in a cell population using the mmRNAs described herein. Such translation can be in vivo, ex vivo, in culture, or in vitro. The cell population is contacted with an effective amount of a composition containing a mmRNA that has at least one nucleoside modification, and a translatable region encoding the recombinant polypeptide. The population is contacted under conditions such that the mmRNA is localized into one or more cells of the cell population and the recombinant polypeptide is translated in the cell from the nucleic acid.

An effective amount of the composition is provided based, at least in part, on the target tissue, target cell type, means of administration, physical characteristics of the nucleic acid (e.g., size, and extent of modified nucleosides), and other determinants. In general, an effective amount of the composition provides efficient protein production in the cell, preferably more efficient than a composition containing a corresponding unmodified nucleic acid. Increased efficiency may be demonstrated by increased cell transfection (i.e., the percentage of cells transfected with the nucleic acid), increased protein translation from the nucleic acid, decreased nucleic acid degradation (as demonstrated, e.g., by increased duration of protein translation from a mmRNA), or reduced innate immune response of the host cell.

Aspects of the invention are directed to methods of inducing in vivo translation of a recombinant polypeptide in a mammalian subject in need thereof. Therein, an effective amount of a composition containing a mmRNA that has at least one nucleoside modification and a translatable region encoding the recombinant polypeptide is administered to the subject using the delivery methods and split dosing regimens described herein. The mmRNA is provided in an amount and under other conditions such that the nucleic acid is localized into a cell of the subject and the recombinant polypeptide is translated in the cell from the mmRNA. The cell in which the mmRNA is localized, or the tissue in which the cell is present, may be targeted with one or more than one rounds of mmRNA administration.

The subject to whom the therapeutic agent is administered suffers from or is at risk of developing a disease, disorder, or deleterious condition. Provided are methods of identifying, diagnosing, and classifying subjects on these bases, which may include clinical diagnosis, biomarker levels, genome-wide association studies (GWAS), and other methods known in the art.

In certain embodiments, the administered mmRNA directs production of one or more recombinant polypeptides that provide a functional activity which is substantially absent in the cell in which the recombinant polypeptide is translated. For example, the missing functional activity may be enzymatic, structural, or gene regulatory in nature. In related embodiments, the administered mmRNA directs production of one or more recombinant polypeptides that increases (e.g., synergistically) a functional activity which is present but substantially deficient in the cell in which the recombinant polypeptide is translated.

In other embodiments, the administered mmRNA directs production of one or more recombinant polypeptides that replace a polypeptide (or multiple polypeptides) that is substantially absent in the cell in which the recombinant polypeptide is translated. Such absence may be due to genetic mutation of the encoding gene or regulatory pathway thereof. In some embodiments, the recombinant polypeptide increases the level of an endogenous protein in the cell to a desirable level; such an increase may bring the level of the endogenous protein from a subnormal level to a normal level or from a normal level to a super-normal level.

Alternatively, the recombinant polypeptide functions to antagonize the activity of an endogenous protein present in, on the surface of, or secreted from the cell. Usually, the activity of the endogenous protein is deleterious to the subject; for example, do to mutation of the endogenous protein resulting in altered activity or localization. Addition-

ally, the recombinant polypeptide antagonizes, directly or indirectly, the activity of a biological moiety present in, on the surface of, or secreted from the cell. Examples of antagonized biological moieties include lipids (e.g., cholesterol), a lipoprotein (e.g., low density lipoprotein), a nucleic acid, a carbohydrate, a protein toxin such as shiga and tetanus toxins, or a small molecule toxin such as botulinum, cholera, and diphtheria toxins. Additionally, the antagonized biological molecule may be an endogenous protein that exhibits an undesirable activity, such as a cytotoxic or cytostatic activity.

The polypeptides encoded by the mmRNA described herein are engineered for localization within the cell, potentially within a specific compartment such as the nucleus, or are engineered for secretion from the cell or translocation to the plasma membrane of the cell.

In one embodiment of the invention are bifunctional mmRNA. As the name implies, bifunctional mmRNA are those having or capable of at least two functions.

The multiple functionalities of bifunctional mmRNAs may be encoded by the mRNA (the function may not manifest until the encoded product is translated) or may be a property of the RNA itself. It may be structural or chemical. Bifunctional modified RNAs may comprise a function that is covalently associated with the RNA or electrostatically associated.

In some embodiments, modified mRNAs and their encoded polypeptides in accordance with the present invention may be used for treatment of any of a variety of diseases, disorders, and/or conditions, including but not limited to one or more of the following: autoimmune disorders (e.g. diabetes, lupus, multiple sclerosis, psoriasis, rheumatoid arthritis); inflammatory disorders (e.g. arthritis, pelvic inflammatory disease); infectious diseases (e.g. viral infections (e.g., HIV, HCV, RSV), bacterial infections, fungal infections, sepsis); neurological disorders (e.g. Alzheimer's disease, Huntington's disease; autism; Duchenne muscular dystrophy); cardiovascular disorders (e.g. atherosclerosis, hypercholesterolemia, thrombosis, clotting disorders, angiogenic disorders such as macular degeneration); proliferative disorders (e.g. cancer, benign neoplasms); respiratory disorders (e.g. chronic obstructive pulmonary disease); digestive disorders (e.g. inflammatory bowel disease, ulcers); musculoskeletal disorders (e.g. fibromyalgia, arthritis); endocrine, metabolic, and nutritional disorders (e.g. diabetes, osteoporosis); urological disorders (e.g. renal disease); psychological disorders (e.g. depression, schizophrenia); skin disorders (e.g. wounds, eczema); blood and lymphatic disorders (e.g. anemia, hemophilia); etc.

Avoidance of the Innate Immune Response

The term "innate immune response" includes a cellular response to exogenous single stranded nucleic acids, generally of viral or bacterial origin, which involves the induction of cytokine expression and release, particularly the interferons, and cell death. Protein synthesis is also reduced during the innate cellular immune response. While it is advantageous to eliminate the innate immune response in a cell, the invention provides modified mRNAs that substantially reduce the immune response, including interferon signaling, without entirely eliminating such a response. In some embodiments, the immune response is reduced by 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99%, 99.9%, or greater than 99.9% as compared to the immune response induced by a corresponding unmodified nucleic acid. Such a reduction can be measured by expression or activity level of Type 1 interferons or the expression of interferon-regulated genes such as the toll-like receptors (e.g., TLR7 and TLR8). Reduction of innate immune response can also be measured by decreased cell death following one or more administrations of modified RNAs to a cell population; e.g., cell death is 10%, 25%, 50%, 75%, 85%, 90%, 95%, or over 95% less than the cell death frequency observed with a corresponding unmodified nucleic acid. Moreover, cell death may affect fewer than 50%, 40%, 30%, 20%, 10%, 5%, 1%, 0.1%, 0.01% or fewer than 0.01% of cells contacted with the mmRNAs.

The invention provides therapeutic methods for the repeated introduction (e.g., transfection) of mmRNAs into a target cell population, e.g., in vitro, ex vivo, or in vivo. The step of contacting the cell population may be repeated one or more times (such as two, three, four, five or more than five times). In some embodiments, the step of contacting the cell population with the mmRNAs is repeated a number of times sufficient such that a predetermined efficiency of protein translation in the cell population is achieved. Given the reduced cytotoxicity of the target cell population provided by the nucleic acid modifications, such repeated transfections are achievable in a diverse array of cell types.

Protein Production

The methods provided herein are useful for enhancing protein product yield in a cell culture process. In a cell culture containing a plurality of host cells, introduction of the modified mRNAs described herein results in increased protein production efficiency relative to a corresponding unmodified nucleic acid. Such increased protein production efficiency can be demonstrated, e.g., by showing increased cell transfection, increased protein translation from the nucleic acid, decreased nucleic acid degradation, and/or reduced innate immune response of the host cell. Protein production can be measured by ELISA, and protein activity can be measured by various functional assays known in the art. The protein production may be generated in a continuous or a fed-batch mammalian process.

Additionally, it is useful to optimize the expression of a specific polypeptide in a cell line or collection of cell lines of potential interest, particularly an engineered protein such as a protein variant of a reference protein having a known activity. In one embodiment, provided is a method of optimizing expression of an engineered protein in a target cell, by providing a plurality of target cell types, and independently contacting with each of the plurality of target cell types a modified mRNA encoding an engineered polypeptide. Additionally, culture conditions may be altered to increase protein production efficiency. Subsequently, the presence and/or level of the engineered polypeptide in the plurality of target cell types is detected and/or quantitated, allowing for the optimization of an engineered polypeptide's expression by selection of an efficient target cell and cell culture conditions relating thereto. Such methods are particularly useful when the engineered polypeptide contains one or more post-translational modifications or has substantial tertiary structure, situations which often complicate efficient protein production.

Gene Silencing

The modified mRNAs described herein are useful to silence (i.e., prevent or substantially reduce) expression of one or more target genes in a cell population. A modified mRNA encoding a polypeptide capable of directing sequence-specific histone H3 methylation is introduced into the cells in the population under conditions such that the polypeptide is translated and reduces gene transcription of a target gene via histone H3 methylation and subsequent heterochromatin formation. In some embodiments, the silencing mechanism is performed on a cell population

present in a mammalian subject. By way of non-limiting example, a useful target gene is a mutated Janus Kinase-2 family member, wherein the mammalian subject expresses the mutant target gene suffers from a myeloproliferative disease resulting from aberrant kinase activity.

Co-administration of modified mRNAs and siRNAs are also provided herein. As demonstrated in yeast, sequence-specific trans silencing is an effective mechanism for altering cell function. Fission yeast require two RNAi complexes for siRNA-mediated heterochromatin assembly: the RNA-induced transcriptional silencing (RITS) complex and the RNA-directed RNA polymerase complex (RDRC) (Motamedi et al. Cell 2004, 119, 789-802). In fission yeast, the RITS complex contains the siRNA binding Argonaute family protein Ago1, a chromodomain protein Chp1, and Tas3. The fission yeast RDRC complex is composed of an RNA-dependent RNA Polymerase Rdp1, a putative RNA helicase Hrr1, and a polyA polymerase family protein Cid12. These two complexes require the Dicer ribonuclease and Clr4 histone H3 methyltransferase for activity. Together, Ago 1 binds siRNA molecules generated through Dicer-mediated cleavage of Rdp1 co-transcriptionally generated dsRNA transcripts and allows for the sequence-specific direct association of Chp1, Tas3, Hrr1, and Clr4 to regions of DNA destined for methylation and histone modification and subsequent compaction into transcriptionally silenced heterochromatin. While this mechanism functions in cis- with centromeric regions of DNA, sequence-specific trans silencing is possible through co-transfection with double-stranded siRNAs for specific regions of DNA and concomitant RNAi-directed silencing of the siRNA ribonuclease Eril (Buhler et al. Cell 2006, 125, 873-886).

Modulation of Biological Pathways

The rapid translation of modified mRNAs introduced into cells provides a desirable mechanism of modulating target biological pathways. Such modulation includes antagonism or agonism of a given pathway. In one embodiment, a method is provided for antagonizing a biological pathway in a cell by contacting the cell with an effective amount of a composition comprising a modified nucleic acid encoding a recombinant polypeptide, under conditions such that the nucleic acid is localized into the cell and the recombinant polypeptide is capable of being translated in the cell from the nucleic acid, wherein the recombinant polypeptide inhibits the activity of a polypeptide functional in the biological pathway. Exemplary biological pathways are those defective in an autoimmune or inflammatory disorder such as multiple sclerosis, rheumatoid arthritis, psoriasis, lupus erythematosus, ankylosing spondylitis colitis, or Crohn's disease; in particular, antagonism of the IL-12 and IL-23 signaling pathways are of particular utility. (See Kikly K, Liu L, Na S, Sedgwick J D (2006) Curr. Opin. Immunol. 18 (6): 670-5).

Further, provided are modified nucleic acids encoding an antagonist for chemokine receptors; chemokine receptors CXCR-4 and CCR-5 are required for, e.g., HIV entry into host cells (et al, (1996) October 3; 383(6599):400).

Alternatively, provided are methods of agonizing a biological pathway in a cell by contacting the cell with an effective amount of a modified nucleic acid encoding a recombinant polypeptide under conditions such that the nucleic acid is localized into the cell and the recombinant polypeptide is capable of being translated in the cell from the nucleic acid, and the recombinant polypeptide induces the activity of a polypeptide functional in the biological pathway. Exemplary agonized biological pathways include pathways that modulate cell fate determination. Such agonization is reversible or, alternatively, irreversible.

Cellular Nucleic Acid Delivery

Methods of the present invention enhance nucleic acid delivery into a cell population, in vivo, ex vivo, or in culture. For example, a cell culture containing a plurality of host cells (e.g., eukaryotic cells such as yeast or mammalian cells) is contacted with a composition that contains an enhanced nucleic acid having at least one nucleoside modification and, optionally, a translatable region. The composition also generally contains a transfection reagent or other compound that increases the efficiency of enhanced nucleic acid uptake into the host cells. The enhanced nucleic acid exhibits enhanced retention in the cell population, relative to a corresponding unmodified nucleic acid. The retention of the enhanced nucleic acid is greater than the retention of the unmodified nucleic acid. In some embodiments, it is at least about 50%, 75%, 90%, 95%, 100%, 150%, 200% or more than 200% greater than the retention of the unmodified nucleic acid. Such retention advantage may be achieved by one round of transfection with the enhanced nucleic acid, or may be obtained following repeated rounds of transfection.

In some embodiments, the enhanced nucleic acid is delivered to a target cell population with one or more additional nucleic acids. Such delivery may be at the same time, or the enhanced nucleic acid is delivered prior to delivery of the one or more additional nucleic acids. The additional one or more nucleic acids may be modified nucleic acids or unmodified nucleic acids. It is understood that the initial presence of the enhanced nucleic acids does not substantially induce an innate immune response of the cell population and, moreover, that the innate immune response will not be activated by the later presence of the unmodified nucleic acids. In this regard, the enhanced nucleic acid may not itself contain a translatable region, if the protein desired to be present in the target cell population is translated from the unmodified nucleic acids.

Expression of Ligand or Receptor on Cell Surface

In some aspects and embodiments of the aspects described herein, the modified RNAs can be used to express a ligand or ligand receptor on the surface of a cell (e.g., a homing moiety). A ligand or ligand receptor moiety attached to a cell surface can permit the cell to have a desired biological interaction with a tissue or an agent in vivo. A ligand can be an antibody, an antibody fragment, an aptamer, a peptide, a vitamin, a carbohydrate, a protein or polypeptide, a receptor, e.g., cell-surface receptor, an adhesion molecule, a glycoprotein, a sugar residue, a therapeutic agent, a drug, a glycosaminoglycan, or any combination thereof. For example, a ligand can be an antibody that recognizes a cancer-cell specific antigen, rendering the cell capable of preferentially interacting with tumor cells to permit tumor-specific localization of a modified cell. A ligand can confer the ability of a cell composition to accumulate in a tissue to be treated, since a preferred ligand may be capable of interacting with a target molecule on the external face of a tissue to be treated. Ligands having limited cross-reactivity to other tissues are generally preferred.

In some cases, a ligand can act as a homing moiety which permits the cell to target to a specific tissue or interact with a specific ligand. Such homing moieties can include, but are not limited to, any member of a specific binding pair, antibodies, monoclonal antibodies, or derivatives or analogs thereof, including without limitation: Fv fragments, single chain Fv (scFv) fragments, Fab' fragments, F(ab')2 fragments, single domain antibodies, camelized antibodies and antibody fragments, humanized antibodies and antibody

fragments, and multivalent versions of the foregoing; multivalent binding reagents including without limitation: monospecific or bispecific antibodies, such as disulfide stabilized Fv fragments, scFv tandems ((SCFV)2 fragments), diabodies, tribodies or tetrabodies, which typically are covalently linked or otherwise stabilized (i.e., leucine zipper or helix stabilized) scFv fragments; and other homing moieties include for example, aptamers, receptors, and fusion proteins.

In some embodiments, the homing moiety may be a surface-bound antibody, which can permit tuning of cell targeting specificity. This is especially useful since highly specific antibodies can be raised against an epitope of interest for the desired targeting site. In one embodiment, multiple antibodies are expressed on the surface of a cell, and each antibody can have a different specificity for a desired target. Such approaches can increase the avidity and specificity of homing interactions.

A skilled artisan can select any homing moiety based on the desired localization or function of the cell, for example an estrogen receptor ligand, such as tamoxifen, can target cells to estrogen-dependent breast cancer cells that have an increased number of estrogen receptors on the cell surface. Other non-limiting examples of ligand/receptor interactions include CCRI (e.g., for treatment of inflamed joint tissues or brain in rheumatoid arthritis, and/or multiple sclerosis), CCR7, CCR8 (e.g., targeting to lymph node tissue), CCR6, CCR9, CCR10 (e.g., to target to intestinal tissue), CCR4, CCR10 (e.g., for targeting to skin), CXCR4 (e.g., for general enhanced transmigration), HCELL (e.g., for treatment of inflammation and inflammatory disorders, bone marrow), Alpha4beta7 (e.g., for intestinal mucosa targeting), VLA-4/VCAM-1 (e.g., targeting to endothelium). In general, any receptor involved in targeting (e.g., cancer metastasis) can be harnessed for use in the methods and compositions described herein.

Mediators of Cell Death

In one embodiment, a modified nucleic acid molecule composition can be used to induce apoptosis in a cell (e.g., a cancer cell) by increasing the expression of a death receptor, a death receptor ligand or a combination thereof. This method can be used to induce cell death in any desired cell and has particular usefulness in the treatment of cancer where cells escape natural apoptotic signals.

Apoptosis can be induced by multiple independent signaling pathways that converge upon a final effector mechanism consisting of multiple interactions between several "death receptors" and their ligands, which belong to the tumor necrosis factor (TNF) receptor/ligand superfamily. The best-characterized death receptors are CD95 ("Fas"), TNFRI (p55), death receptor 3 (DR3 or Apo3/TRAMO), DR4 and DR5 (apo2-TRAIL-R2). The final effector mechanism of apoptosis may be the activation of a series of proteinases designated as caspases. The activation of these caspases results in the cleavage of a series of vital cellular proteins and cell death. The molecular mechanism of death receptors/ligands-induced apoptosis is well known in the art. For example, Fas/FasL-mediated apoptosis is induced by binding of three FasL molecules which induces trimerization of Fas receptor via C-terminus death domains (DDs), which in turn recruits an adapter protein FADD (Fas-associated protein with death domain) and Caspase-8. The oligomerization of this trimolecular complex, Fas/FAIDD/caspase-8, results in proteolytic cleavage of proenzyme caspase-8 into active caspase-8 that, in turn, initiates the apoptosis process by activating other downstream caspases through proteolysis, including caspase-3. Death ligands in general are apoptotic when formed into trimers or higher order of structures. As monomers, they may serve as antiapoptotic agents by competing with the trimers for binding to the death receptors.

In one embodiment, the modified nucleic acid molecule composition encodes for a death receptor (e.g., Fas, TRAIL, TRAMO, TNFR, TLR etc). Cells made to express a death receptor by transfection of modified RNA become susceptible to death induced by the ligand that activates that receptor. Similarly, cells made to express a death ligand, e.g., on their surface, will induce death of cells with the receptor when the transfected cell contacts the target cell. In another embodiment, the modified RNA composition encodes for a death receptor ligand (e.g., FasL, TNF, etc). In another embodiment, the modified RNA composition encodes a caspase (e.g., caspase 3, caspase 8, caspase 9 etc). Where cancer cells often exhibit a failure to properly differentiate to a non-proliferative or controlled proliferative form, in another embodiment, the synthetic, modified RNA composition encodes for both a death receptor and its appropriate activating ligand. In another embodiment, the synthetic, modified RNA composition encodes for a differentiation factor that when expressed in the cancer cell, such as a cancer stem cell, will induce the cell to differentiate to a non-pathogenic or nonself-renewing phenotype (e.g., reduced cell growth rate, reduced cell division etc) or to induce the cell to enter a dormant cell phase (e.g., G_0 resting phase).

One of skill in the art will appreciate that the use of apoptosis-inducing techniques may require that the modified nucleic acid molecules are appropriately targeted to e.g., tumor cells to prevent unwanted wide-spread cell death. Thus, one can use a delivery mechanism (e.g., attached ligand or antibody, targeted liposome etc) that recognizes a cancer antigen such that the modified nucleic acid molecules are expressed only in cancer cells.

Formulations of Modified mRNAs

Provided herein are formulations containing an effective amount of an mmRNA.

In certain embodiments, the formulations include one or more cell penetration agents, e.g., transfection agents. In one specific embodiment, an mmRNA is mixed or admixed with a transfection agent (or mixture thereof) and the resulting mixture is employed to transfect cells. Preferred transfection agents are cationic lipid compositions, particularly monovalent and polyvalent cationic lipid compositions, more particularly LIPOFECTIN®, LIPOFECTACE®, LIPOFECTAMINE™, CELLFECTIN®, DMRIE-C, DMRIE, DOTAP, DOSPA, and DOSPER, and dendrimer compositions, particularly G5-G10 dendrimers, including dense star dendrimers, PAMAM dendrimers, grafted dendrimers, and dendrimers known as dendrigrafts and SUPERFECT®.

In a second specific transfection method, a ribonucleic acid is conjugated to a nucleic acid-binding group, for example a polyamine and more particularly a spermine, which is then introduced into the cell or admixed with a transfection agent (or mixture thereof) and the resulting mixture is employed to transfect cells. In a third specific embodiment, a mixture of one or more transfection-enhancing peptides, proteins, or protein fragments, including fusagenic peptides or proteins, transport or trafficking peptides or proteins, receptor-ligand peptides or proteins, or nuclear localization peptides or proteins and/or their modified analogs (e.g., spermine modified peptides or proteins) or combinations thereof are mixed with and complexed with a ribonucleic acid to be introduced into a cell, optionally being admixed with transfection agent and the resulting mixture is

employed to transfect cells. Further, a component of a transfection agent (e.g., lipids, cationic lipids or dendrimers) is covalently conjugated to selected peptides, proteins, or protein fragments directly or via a linking or spacer group. Of particular interest in this embodiment are peptides or proteins that are fusagenic, membrane-permeabilizing, transport or trafficking, or which function for cell-targeting. The peptide- or protein-transfection agent complex is combined with a ribonucleic acid and employed for transfection.

In certain embodiments, the formulations include a pharmaceutically acceptable carrier that causes the effective amount of mmRNA to be substantially retained in a target tissue containing the cell.

In certain embodiments, the formulation may include at least an mmRNA and a delivery agent. In some embodiments, the delivery agent may comprise lipidoid-based formulations allowed for localized and systemic delivery of mmRNA.

Also provided are compositions for generation of an in vivo depot containing an engineered ribonucleotide. For example, the composition contains a bioerodible, biocompatible polymer, a solvent present in an amount effective to plasticize the polymer and form a gel therewith, and an engineered ribonucleic acid. In certain embodiments the composition also includes a cell penetration agent as described herein. In other embodiments, the composition also contains a thixotropic amount of a thixotropic agent mixable with the polymer so as to be effective to form a thixotropic composition. Further compositions include a stabilizing agent, a bulking agent, a chelating agent, or a buffering agent.

In other embodiments, provided are sustained-release delivery depots, such as for administration of a mmRNA to an environment (meaning an organ or tissue site) in a patient. Such depots generally contain a mmRNA and a flexible chain polymer where both the mmRNA and the flexible chain polymer are entrapped within a porous matrix of a crosslinked matrix protein. Usually, the pore size is less than 1 mm, such as 900 nm, 800 nm, 700 nm, 600 nm, 500 nm, 400 nm, 300 nm, 200 nm, 100 nm, or less than 100 nm. Usually the flexible chain polymer is hydrophilic. Usually the flexible chain polymer has a molecular weight of at least 50 kDa, such as 75 kDa, 100 kDa, 150 kDa, 200 kDa, 250 kDa, 300 kDa, 400 kDa, 500 kDa, or greater than 500 kDa. Usually the flexible chain polymer has a persistence length of less than 10%, such as 9, 8, 7, 6, 5, 4, 3, 2, 1 or less than 1% of the persistence length of the matrix protein. Usually the flexible chain polymer has a charge similar to that of the matrix protein. In some embodiments, the flexible chain polymer alters the effective pore size of a matrix of crosslinked matrix protein to a size capable of sustaining the diffusion of the mmRNA from the matrix into a surrounding tissue comprising a cell into which the mmRNA is capable of entering.

Formulation Using Lipidoids

The pharmaceutical compositions described herein include lipidoid-based formulations allowing for localized and systemic delivery of mmRNA. The synthesis of lipidoids has been extensively described and formulations containing these compounds are particularly suited for delivery of polynucleotides (see Mahon et al., Bioconjug Chem. 2010 21:1448-1454; Schroeder et al., J Intern Med. 2010 267:9-21; Akinc et al., Nat Biotechnol. 2008 26:561-569; Love et al., Proc Natl Acad Sci USA. 2010 107:1864-1869; Siegwart et al., Proc Natl Acad Sci USA. 2011 108:12996-3001; all of which are incorporated herein by reference in their entireties).

According to the present invention, complexes, micelles, liposomes or particles can be prepared containing these lipidoids and therefore, result in an effective delivery of mmRNA, as judged by the production of an encoded protein, following the injection of an mmRNA-formulated lipidoids via localized and systemic routes of administration. Modified mRNA-lipidoid complexes can be administered by various means disclosed herein.

The characteristics of optimized lipidoid formulations for intramuscular or subcutaneous routes may vary significantly depending on the target cell type and the ability of formulations to diffuse through the extracellular matrix into the blood stream. While a particle size of less than 150 nm may be desired for effective hepatocyte delivery due to the size of the endothelial fenestrae (see, Akinc et al., Mol Ther. 2009 17:872-879 herein incorporated by reference), use of lipidoid oligonucleotides to deliver the formulation to other cells types including, but not limited to, endothelial cells, myeloid cells, and muscle cells may not be similarly size-limited.

In one aspect, effective delivery to myeloid cells, such as monocytes, lipidoid formulations may have a similar component molar ratio. Different ratios of lipidoids and other components including, but not limited to, disteroylphosphatidyl choline, cholesterol and PEG-DMG, may be used to optimize the formulation of the mmRNA molecule for delivery to different cell types including, but not limited to, hepatocytes, myeloid cells, muscle cells, etc. For example, the component molar ratio may include, but is not limited to, 50% lipid, 10% disteroylphosphatidyl choline, 38.5% cholesterol, and % 1.5 PEG. The lipid may be selected from, but is not limited to, DLin-DMA, DLin-K-DMA, DLin-KC2-DMA, 98N12-5, C12-200 (including variants and derivatives), DLin-MC3-DMA and analogs thereof. The use of lipidoid formulations for the localized delivery of nucleic acids to cells (such as, but not limited to, adipose cells and muscle cells) via either subcutaneous or intramuscular delivery, may also not require all of the formulation components which may be required for systemic delivery, and as such may comprise the lipidoid and the mmRNA.

In a further embodiment, combinations of different lipidoids may be used to improve the efficacy of mmRNA-directed protein.

According to the present invention, modified mRNA may be formulated by mixing the mmRNA with the lipidoid at a set ratio prior to addition to cells. In vivo formulations may require the addition of extra ingredients to facilitate circulation throughout the body. To test the ability of these lipidoids to form particles suitable for in vivo work, a standard formulation process used for siRNA-lipidoid formulations may be used as a starting point. Initial mmRNA-lipidoid formulations consist of particles composed of 42% lipidoid, 48% cholesterol and 10% PEG, with further optimization of ratios possible. After formation of the particle, mmRNA is added and allowed to integrate with the complex. The encapsulation efficiency is determined using a standard dye exclusion assays.

In vivo delivery of nucleic acids may be affected by many parameters, including, but not limited to, the formulation composition, nature of particle PEGylation, degree of loading, oligonucleotide to lipid ratio, and biophysical parameters such as particle size (Akinc et al., Mol Ther. 2009 17:872-879; herein incorporated by reference in its entirety). As an example, small changes in the anchor chain length of poly(ethylene glycol) (PEG) lipids may result in significant effects on in vivo efficacy. Formulations with the different lipidoids, including, but not limited to penta[3-(1-laurylami-

nopropionyl)]-triethylenetetramine hydrochloride (TETA-5LAP; aka 98N12-5, see Murugaiah et al., Analytical Biochemistry, 401:61 (2010)), C12-200 (including derivatives and variants), MD1, DLin-DMA, DLin-K-DMA, DLin-KC2-DMA and DLin-MC3-DMA (see FIG. **1**), can be tested for in vivo activity.

The lipidoid referred to herein as "98N12-5" is disclosed by Akinc et al., Mol Ther. 2009 17:872-879 and is incorporated by reference in its entirety. (See FIG. **1**)

The lipidoid referred to herein as "C12-200" is disclosed by Love et al., Proc Natl Acad Sci USA. 2010 107:1864-1869 (see FIG. **1**) and Liu and Huang, Molecular Therapy. 2010 669-670 (see FIG. **1**); both of which are herein incorporated by reference in their entirety. The lipidoid formulations can include particles comprising either 3 or 4 or more components in addition to polynucleotide, primary construct, or mmRNA. As an example, formulations with certain lipidoids, include, but are not limited to, 98N12-5 and may contain 42% lipidoid, 48% cholesterol and 10% PEG (C14 alkyl chain length). As another example, formulations with certain lipidoids, include, but are not limited to, C12-200 and may contain 50% lipidoid, 10% disteroylphosphatidyl choline, 38.5% cholesterol, and 1.5% PEG-DMG.

The ratio of mmRNA to lipidoid used to test for in vitro transfection is tested empirically at different lipidoid: mmRNA ratios. Previous work using siRNA and lipidoids have utilized 2.5:1, 5:1, 10:1, and 15:1 lipidoid:siRNA wt:wt ratios. Given the longer length of mmRNA relative to siRNA, a lower wt:wt ratio of lipidoid to mmRNA is likely to be effective. In addition, for comparison mmRNA are also formulated using RNAiMax (Invitrogen, Carlsbad, Calif.) or TRANSIT-mRNA (Mirus Bio, Madison Wis.) cationic lipid delivery vehicles.

The ability of lipidoid-formulated mmRNA to express the desired protein product can be confirmed by luminescence for luciferase expression, flow cytometry for expression, and by ELISA for secretion.

The expression of mmRNA-encoded proteins can be assessed both within the muscle or subcutaneous tissue and systemically in blood and other organs and fluids such as the liver and spleen, urine, saliva, etc.

For example, single dose studies allow an assessment of the magnitude, dose responsiveness, and longevity of expression of the desired product. After formulation of mmRNA with the lipidoid formulations, as described previously, animals are divided into groups receiving either a saline formulation, or a lipidoid-formulation containing one of several different mmRNA. Prior to injection, mmRNA-containing lipidoid formulations are diluted in PBS and animals administered a single intramuscular dose of formulated mmRNA ranging from 50 mg/kg to doses as low as 1 ng/kg with a preferred range to be 10 mg/kg to 100 ng/kg. If the animal tested is a mouse the maximum dose can be roughly 1 mg mmRNA or as low as 0.02 ng mmRNA if administered once into the hind limb. Likewise for subcutaneous administration, mmRNA-containing lipidoid formulations are diluted in PBS before the animals are administered a single subcutaneous dose of formulated mmRNA ranging from 400 mg/kg- to doses as low as 1 ng/kg. A preferred dosage range comprises 80 mg/kg to 100 ng/kg. If the animal tested is a mouse, the maximum dose administered can be roughly 8 mg mmRNA or as low as 0.02 ng mmRNA if the dose is administered once subcutaneously.

It is preferred that the volume of a single intramuscular injection is maximally 0.025 ml and of a single subcutaneous injection is maximally 0.2 ml for a 20 gram mouse. The dose of the mmRNA administered to the animal is calculated depending on the body weight of the animal. At various points in time points following the administration of the mmRNA-lipidoid, serum, tissues, and tissue lysates can be obtained and the level of the mmRNA-encoded product determined. The ability of lipidoid-formulated mmRNA to express the desired protein product can be confirmed by luminescence for luciferase expression, flow cytometry, and by ELISA.

Additional studies for a multi-dose regimen can also be performed to determine the maximal expression using mmRNA, to evaluate the saturability of the mmRNA-driven expression (achieved by giving a control and active mmRNA formulation in parallel or in sequence), and to determine the feasibility of repeat drug administration (by giving mmRNA in doses separated by weeks or months and then determining whether expression level is affected by factors such as immunogenicity).

Administration

The present invention provides methods comprising administering modified mRNAs and or complexes in accordance with the invention to a subject in need thereof. mmRNA or complexes, or pharmaceutical, imaging, diagnostic, or prophylactic compositions thereof, may be administered to a subject using any amount and any route of administration which may be effective for preventing, treating, diagnosing, or imaging a disease, disorder, and/or condition (e.g., a disease, disorder, and/or condition relating to working memory deficits). The exact amount required will vary from subject to subject, depending on factors such as, but not limited to, the species, age, and general condition of the subject, the severity of the disease, the particular composition, its mode of administration, its mode of activity, and the like.

mmRNA to be delivered and/or pharmaceutical, prophylactic, diagnostic, or imaging compositions thereof may be administered to animals, such as mammals (e.g., humans, domesticated animals, cats, dogs, mice, rats, etc.). In some embodiments, pharmaceutical, prophylactic, diagnostic, or imaging compositions thereof are administered to humans.

mmRNA may be administered by any route. In some embodiments, mmRNA are administered by one or more of a variety of routes, including, but not limited to, local, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, subcutaneous, intraventricular, transdermal, interdermal, rectal, intravaginal, intraperitoneal, topical (e.g. by powders, ointments, creams, gels, lotions, and/or drops), mucosal, nasal, buccal, enteral, vitreal, intratumoral, sublingual; by intratracheal instillation, bronchial instillation, and/or inhalation; as an oral spray, nasal spray, and/or aerosol, and/or through a portal vein catheter.

In some embodiments, mmRNA are administered by systemic intravenous injection. In specific embodiments, mmRNA may be administered intravenously and/or orally. In specific embodiments, mmRNA may be administered in a way which allows the mmRNA to cross the blood-brain barrier, vascular barrier, or other epithelial barrier.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing agents, wetting agents, and/or suspending agents. Sterile injectable preparations may be sterile injectable solutions, suspensions, and/or emulsions in nontoxic parenterally acceptable diluents and/or solvents, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P., and isotonic sodium chloride solution. Sterile, fixed oils are conventionally employed as a solvent or suspending

medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. Fatty acids such as oleic acid can be used in the preparation of injectables.

Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, and/or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

Dosage forms for local, topical and/or transdermal administration of a composition may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants and/or patches. Additionally, the present invention contemplates the use of transdermal patches, which often have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms may be prepared, for example, by dissolving and/or dispensing the compound in the proper medium. Alternatively or additionally, rate may be controlled by either providing a rate controlling membrane and/or by dispersing the compound in a polymer matrix and/or gel.

Formulations suitable for topical administration include, but are not limited to, liquid and/or semi liquid preparations such as liniments, lotions, oil in water and/or water in oil emulsions such as creams, ointments and/or pastes, and/or solutions and/or suspensions. Topically-administrable formulations may, for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of active ingredient may be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

A pharmaceutical composition may be prepared, packaged, and/or sold in a formulation suitable for ophthalmic administration. Such formulations may, for example, be in the form of eye drops including, for example, a 0.1/1.0% (w/w) solution and/or suspension of the active ingredient in an aqueous or oily liquid excipient. Such drops may further comprise buffering agents, salts, and/or one or more other of any additional ingredients described herein. Other opthalmically-administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form and/or in a liposomal preparation. Ear drops and/or eye drops are contemplated as being within the scope of this invention.

In general the most appropriate route of administration will depend upon a variety of factors including the nature of the mmRNA to be delivered (e.g., its stability in the environment of the gastrointestinal tract, bloodstream, etc.), the condition of the patient (e.g., whether the patient is able to tolerate particular routes of administration), etc. The invention encompasses the delivery of the mmRNA by any appropriate route taking into consideration likely advances in the sciences of drug delivery.

In certain embodiments, compositions in accordance with the present invention may be administered at dosage levels sufficient to deliver from about 0.0001 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, from about 0.1 mg/kg to about 40 mg/kg, from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, or from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic, diagnostic or prophylactic effect. The desired dosage may be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage may be delivered using multiple administrations (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations). When multiple administration is employed, split dosing regimens such as those described herein may be used.

According to the present invention, it has been discovered that administration of mmRNA in split-dose regimens produce higher levels of proteins in mammalian subjects. As used herein, a "split dose" is the division of single unit dose or total daily dose into two or more doses. As used herein, a "single unit dose" is a dose of any therapeutic administered in one dose/at one time/single route/single point of contact, i.e., single administration event. As used herein, a "total daily dose" is an amount given or prescribed in 24 hr period. It may be administered as a single unit dose. In one embodiment, the mmRNA of the present invention are administered to a subject in split doses. The mmRNA may be formulated in buffer only or in a formulation described herein.

Modified nucleic acid molecules or complexes may be used or administered in combination with one or more other therapeutic, prophylactic, diagnostic, or imaging agents. By "in combination with," it is not intended to imply that the agents must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope of the present disclosure. Compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. In some embodiments, the present disclosure encompasses the delivery of pharmaceutical, prophylactic, diagnostic, or imaging compositions in combination with agents that may improve their bioavailability, reduce and/or modify their metabolism, inhibit their excretion, and/or modify their distribution within the body.

It will further be appreciated that therapeutically, prophylactically, diagnostically, or imaging active agents utilized in combination may be administered together in a single composition or administered separately in different compositions. In general, it is expected that agents utilized in combination with be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually. In one embodiment, the combinations, each or together may be administered according to the split dosing regimens described herein.

The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, a composition useful for treating cancer in accordance with the invention may be administered concurrently with a chemotherapeutic agent), or they may achieve different effects (e.g., control of any adverse effects).

Compositions containing mmRNAs are formulated for administration intramuscularly, transarterially, intraocularly, vaginally, rectally, intraperitoneally, intravenously, intranasally, subcutaneously, endoscopically, transdermally, intramuscularly, intraventricularly, intradermally, intrathecally, topically (e.g. by powders, ointments, creams, gels, lotions, and/or drops), mucosally, nasal, enterally, intratumorally, by

intratracheal instillation, bronchial instillation, and/or inhalation; nasal spray and/or aerosol, and/or through a portal vein catheter.

The compositions may also be formulated for direct delivery to an organ or tissue in any of several ways in the art including, but not limited to, direct soaking or bathing, via a catheter, by gels, powder, ointments, creams, gels, lotions, and/or drops, by using substrates such as fabric or biodegradable materials coated or impregnated with the compositions, and the like. In some embodiments, the composition is formulated for extended release. In specific embodiments, mmRNA molecules or complexes, and/or pharmaceutical, prophylactic, diagnostic, or imaging compositions thereof, may be administered in a way which allows the mmRNA molecules or complex to cross the blood-brain barrier, vascular barrier, or other epithelial barrier.

In some aspects of the invention, the nucleic acids (particularly ribonucleic acids encoding polypeptides) are spatially retained within or proximal to a target tissue. Provided are method of providing a composition to a target tissue of a mammalian subject by contacting the target tissue (which contains one or more target cells) with the composition under conditions such that the composition, in particular the nucleic acid component(s) of the composition, is substantially retained in the target tissue, meaning that at least 10, 20, 30, 40, 50, 60, 70, 80, 85, 90, 95, 96, 97, 98, 99, 99.9, 99.99 or greater than 99.99% of the composition is retained in the target tissue. Advantageously, retention is determined by measuring the amount of the nucleic acid present in the composition that enters one or more target cells. For example, at least 1, 5, 10, 20, 30, 40, 50, 60, 70, 80, 85, 90, 95, 96, 97, 98, 99, 99.9, 99.99 or greater than 99.99% of the nucleic acids administered to the subject are present intracellularly at a period of time following administration. For example, intramuscular injection to a mammalian subject is performed using an aqueous composition containing a ribonucleic acid and a transfection reagent, and retention of the composition is determined by measuring the amount of the ribonucleic acid present in the muscle cells.

Aspects of the invention are directed to methods of providing a composition to a target tissue of a mammalian subject, by contacting the target tissue (containing one or more target cells) with the composition under conditions such that the composition is substantially retained in the target tissue. The composition contains an effective amount of a ribonucleic acid engineered to avoid an innate immune response of a cell into which the ribonucleic acid enters, where the ribonucleic acid contains a nucleotide sequence encoding a polypeptide of interest, under conditions such that the polypeptide of interest is produced in at least one target cell. The compositions generally contain a cell penetration agent, although "naked" nucleic acid (such as nucleic acids without a cell penetration agent or other agent) is also contemplated, and a pharmaceutically acceptable carrier.

In some circumstances, the amount of a protein produced by cells in a tissue is desirably increased. Preferably, this increase in protein production is spatially restricted to cells within the target tissue. Thus, provided are methods of increasing production of a protein of interest in a tissue of a mammalian subject. A composition is provided that contains a ribonucleic acid that is engineered to avoid an innate immune response of a cell into which the ribonucleic acid enters and encodes the polypeptide of interest and the composition is characterized in that a unit quantity of composition has been determined to produce the polypeptide of interest in a substantial percentage of cells contained within a predetermined volume of the target tissue. In some embodiments, the composition includes a plurality of different ribonucleic acids, where one or more than one of the ribonucleic acids is engineered to avoid an innate immune response of a cell into which the ribonucleic acid enters, and where one or more than one of the ribonucleic acids encodes a polypeptide of interest. Optionally, the composition also contains a cell penetration agent to assist in the intracellular delivery of the ribonucleic acid. A determination is made of the dose of the composition required to produce the polypeptide of interest in a substantial percentage of cells contained within the predetermined volume of the target tissue (generally, without inducing significant production of the polypeptide of interest in tissue adjacent to the predetermined volume, or distally to the target tissue). Subsequent to this determination, the determined dose is introduced directly into the tissue of the mammalian subject.

Formulations which may be administered intramuscularly and/or subcutaneously may include, but are not limited to, polymers, copolymers, and gels. The polymers, copolymers and/or gels may further be adjusted to modify release kinetics by adjusting factors such as, but not limited to, molecular weight, particle size, payload and/or ratio of the monomers. As a non-limiting example, formulations administered intramuscularly and/or subcutaneously may include a copolymer such as poly(lactic-co-glycolic acid).

Localized delivery of the compositions described herein may be administered by methods such as, but not limited to, topical delivery, ocular delivery, transdermal delivery, and the like. The composition may also be administered locally to a part of the body not normally available for localized delivery such as, but not limited to, when a subject's body is open to the environment during treatment. The composition may further be delivered by bathing, soaking and/or surrounding the body part with the composition.

However, the present disclosure encompasses the delivery of mmRNA molecules or complexes, and/or pharmaceutical, prophylactic, diagnostic, or imaging compositions thereof, by any appropriate route taking into consideration likely advances in the sciences of drug delivery.

The level or concentration of a mmRNA may be characterized using exosomes. A level or concentration of the mmRNA in exosomes can represent an expression level, presence, absence, truncation or alteration of the mmRNA. The level or concentration may be determined by a method such as, but not limited to, an assay using construct specific probes, cytometry, qRT-PCR, realtime PCR, PCR, flow cytometry, electrophoresis, mass spectrometry, or combinations thereof. Further, the level or concentration may be associated with a clinical phenotype. For analysis, the exosome may be isolated by a method such as, but not limited to, immunohistochemcial methods such as enzyme linked immunosorbant assay (ELISA) methods, size exclusion chromatography, density gradient centrifugation, differential centrifugation, nanomembrane ultrafiltration, immunoabsorbent capture, affinity purification, microfluidic separation, or combinations thereof.

Pharmaceutical Compositions

When administered to a subject the pharmaceutical compositions described herein may provide proteins which have been generated from modified mRNAs. Pharmaceutical compositions may optionally comprise one or more additional therapeutically active substances. In accordance with some embodiments, a method of administering pharmaceutical compositions comprising one or more proteins to be delivered to a subject in need thereof is provided. In some

embodiments, compositions are administered to human subjects. In a further embodiment, the compositions are administered to a subject who is a patient.

Pharmaceutical compositions may optionally comprise one or more additional therapeutically active substances.

In some embodiments, compositions are administered to humans. For the purposes of the present disclosure, the phrase "active ingredient" generally refers to a mmRNA to be delivered as described herein.

Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with merely ordinary, if any, experimentation. Subjects to which administration of the pharmaceutical compositions is contemplated include, but are not limited to, humans and/or other primates; mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, cats, dogs, mice, and/or rats; and/or birds, including commercially relevant birds such as chickens, ducks, geese, and/or turkeys.

Formulations of the pharmaceutical compositions described herein may be prepared by any method known or hereafter developed in the art of pharmacology. In general, such preparatory methods include the step of bringing the active ingredient into association with an excipient and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single- or multi-dose unit.

A pharmaceutical composition in accordance with the invention may be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" is discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition in accordance with the invention will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

Pharmaceutical formulations may additionally comprise a pharmaceutically acceptable excipient, which, as used herein, includes any and all solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's *The Science and Practice of Pharmacy,* 21st Edition, A. R. Gennaro (Lippincott, Williams & Wilkins, Baltimore, Md., 2006; incorporated herein by reference) discloses various excipients used in formulating pharmaceutical compositions and known techniques for the preparation thereof. Except insofar as any conventional excipient medium is incompatible with a substance or its derivatives, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition, its use is contemplated to be within the scope of this invention.

In some embodiments, a pharmaceutically acceptable excipient is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% pure. In some embodiments, an excipient is approved for use in humans and for veterinary use.

In some embodiments, an excipient is approved by United States Food and Drug Administration. In some embodiments, an excipient is pharmaceutical grade. In some embodiments, an excipient meets the standards of the United States Pharmacopoeia (USP), the European Pharmacopoeia (EP), the British Pharmacopoeia, and/or the International Pharmacopoeia.

Pharmaceutically acceptable excipients used in the manufacture of pharmaceutical compositions include, but are not limited to, inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Such excipients may optionally be included in pharmaceutical formulations. Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and/or perfuming agents can be present in the composition, according to the judgment of the formulator.

Exemplary diluents include, but are not limited to, calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, etc., and/or combinations thereof.

Exemplary granulating and/or dispersing agents include, but are not limited to, potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinylpyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, etc., and/or combinations thereof.

Exemplary surface active agents and/or emulsifiers include, but are not limited to, natural emulsifiers (e.g. acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (e.g. bentonite [aluminum silicate] and Veegum® [magnesium aluminum silicate]), long chain amino acid derivatives, high molecular weight alcohols (e.g. stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (e.g. carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (e.g. carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (e.g. polyoxyethylene sorbitan monolaurate [TWEEN®20], polyoxyethylene sorbitan [TWEEN®60], polyoxyethylene sorbitan monooleate [TWEEN®80], sorbi-

tan monopalmitate [SPAN®40], sorbitan monostearate [SPAN®60], sorbitan tristearate [SPAN®65], glyceryl monooleate, sorbitan monooleate [SPAN®80]), polyoxyethylene esters (e.g. polyoxyethylene monostearate [MYRJ®45], polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and SOLUTOL®), sucrose fatty acid esters, polyethylene glycol fatty acid esters (e.g. CREMOPHOR®), polyoxyethylene ethers, (e.g. polyoxyethylene lauryl ether [BRIJ®30]), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, PLURONIC®F 68, POLOXAMER®188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, etc. and/or combinations thereof.

Exemplary binding agents include, but are not limited to, starch (e.g. cornstarch and starch paste); gelatin; sugars (e.g. sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol); natural and synthetic gums (e.g. acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (VEEGUM®), and larch arabogalactan); alginates; polyethylene oxide; polyethylene glycol; inorganic calcium salts; silicic acid; polymethacrylates; waxes; water; alcohol; etc.; and combinations thereof.

Exemplary preservatives may include, but are not limited to, antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and/or other preservatives. Exemplary antioxidants include, but are not limited to, alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and/or sodium sulfite. Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA), citric acid monohydrate, disodium edetate, dipotassium edetate, edetic acid, fumaric acid, malic acid, phosphoric acid, sodium edetate, tartaric acid, and/or trisodium edetate. Exemplary antimicrobial preservatives include, but are not limited to, benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and/or thimerosal. Exemplary antifungal preservatives include, but are not limited to, butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and/or sorbic acid. Exemplary alcohol preservatives include, but are not limited to, ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and/or phenylethyl alcohol. Exemplary acidic preservatives include, but are not limited to, vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and/or phytic acid. Other preservatives include, but are not limited to, tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, GLYDANT PLUS®, PHENONIP®, methylparaben, GERMALL®115, GERMABEN®II, NEOLONE™, KATHON™, and/or EUXYL®.

Exemplary buffering agents include, but are not limited to, citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, etc., and/or combinations thereof.

Exemplary lubricating agents include, but are not limited to, magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, etc., and combinations thereof.

Exemplary oils include, but are not limited to, almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and/or combinations thereof.

Liquid dosage forms for oral and parenteral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and/or elixirs. In addition to active ingredients, liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and/or perfuming agents. In certain embodiments for parenteral administration, compositions are mixed with solubilizing agents such as Cremophor®, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and/or combinations thereof.

General considerations in the formulation and/or manufacture of pharmaceutical agents may be found, for example, in *Remington: The Science and Practice of Pharmacy* 21st ed., Lippincott Williams & Wilkins, 2005 (incorporated herein by reference).

In order to prolong the effect of an active ingredient, it is often desirable to slow the absorption of the active ingredient from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly (orthoesters) and poly(anhydrides). Depot injectable formulations are prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

Compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing compositions with suitable non-irritating excipients such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active ingredient. Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, an active ingredient is mixed with at least one inert, pharmaceutically acceptable excipient such as sodium citrate or dicalcium phosphate and/or fillers or extenders (e.g. starches, lactose, sucrose, glucose, mannitol, and silicic acid), binders (e.g. carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia), humectants (e.g. glycerol), disintegrating agents (e.g. agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate), solution retarding agents (e.g. paraffin), absorption accelerators (e.g. quaternary ammonium compounds), wetting agents (e.g. cetyl alcohol and glycerol monostearate), absorbents (e.g. kaolin and bentonite clay), and lubricants (e.g. talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate), and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may comprise buffering agents.

Solid compositions of a similar type may be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. Solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. Solid compositions of a similar type may be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

Dosage forms for topical and/or transdermal administration of a composition may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants and/or patches. Generally, an active ingredient is admixed under sterile conditions with a pharmaceutically acceptable excipient and/or any needed preservatives and/or buffers as may be required. Topically-administrable formulations may, for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of active ingredient may be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

A pharmaceutical composition may be prepared, packaged, and/or sold in a formulation suitable for pulmonary administration via the buccal cavity. Such a formulation may comprise dry particles which comprise the active ingredient and which have a diameter in the range from about 0.5 nm to about 7 nm or from about 1 nm to about 6 nm. Such compositions are suitably in the form of dry powders for administration using a device comprising a dry powder reservoir to which a stream of propellant may be directed to disperse the powder and/or using a self propelling solvent/powder dispensing container such as a device comprising the active ingredient dissolved and/or suspended in a low-boiling propellant in a sealed container. Such powders comprise particles wherein at least 98% of the particles by weight have a diameter greater than 0.5 nm and at least 95% of the particles by number have a diameter less than 7 nm. Alternatively, at least 95% of the particles by weight have a diameter greater than 1 nm and at least 90% of the particles by number have a diameter less than 6 nm. Dry powder compositions may include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

Low boiling propellants generally include liquid propellants having a boiling point of below 65° F. at atmospheric pressure. Generally the propellant may constitute 50% to 99.9% (w/w) of the composition, and active ingredient may constitute 0.1% to 20% (w/w) of the composition. A propellant may further comprise additional ingredients such as a liquid non-ionic and/or solid anionic surfactant and/or a solid diluent (which may have a particle size of the same order as particles comprising the active ingredient).

Pharmaceutical compositions formulated for pulmonary delivery may provide an active ingredient in the form of droplets of a solution and/or suspension. Such formulations may be prepared, packaged, and/or sold as aqueous and/or dilute alcoholic solutions and/or suspensions, optionally sterile, comprising active ingredient, and may conveniently be administered using any nebulization and/or atomization device. Such formulations may further comprise one or more additional ingredients including, but not limited to, a flavoring agent such as saccharin sodium, a volatile oil, a buffering agent, a surface active agent, and/or a preservative such as methylhydroxybenzoate. Droplets provided by this route of administration may have an average diameter in the range from about 0.1 nm to about 200 nm.

Formulations described herein as being useful for pulmonary delivery are useful for intranasal delivery of a pharmaceutical composition. Another formulation suitable for intranasal administration is a coarse powder comprising the active ingredient and having an average particle from about 0.2 μm to 500 μm. Such a formulation is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close to the nose.

Formulations suitable for nasal administration may, for example, comprise from about as little as 0.1% (w/w) and as much as 100% (w/w) of active ingredient, and may comprise one or more of the additional ingredients described herein. A pharmaceutical composition may be prepared, packaged, and/or sold in a formulation suitable for buccal administration. Such formulations may, for example, be in the form of tablets and/or lozenges made using conventional methods, and may, for example, 0.1% to 20% (w/w) active ingredient, the balance comprising an orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations suitable for buccal administration may comprise a powder and/or an aerosolized and/or atomized solution and/or suspension comprising active ingredient. Such powdered, aerosolized, and/or aerosolized formulations, when dispersed, may have an average particle and/or droplet size in the range from about 0.1 nm to about 200 nm, and may further comprise one or more of any additional ingredients described herein

Properties of the Pharmaceutical Compositions

The pharmaceutical compositions described herein can be characterized by one or more of the following properties:

Bioavailability

The mmRNA molecules, when formulated into a composition with a delivery agent as described herein, can exhibit an increase in bioavailability as compared to a composition lacking a delivery agent as described herein. As used herein, the term "bioavailability" refers to the systemic availability of a given amount of a mmRNA molecule administered to a mammal. Bioavailability can be assessed by measuring the area under the curve (AUC) or the maximum serum or plasma concentration (C_{max}) of the unchanged form of a compound following administration of the compound to a mammal. AUC is a determination of the area under the curve plotting the serum or plasma concentration of a compound along the ordinate (Y-axis) against time along the abscissa (X-axis). Generally, the AUC for a particular compound can be calculated using methods known to those of ordinary skill in the art and as described in G. S. Banker, Modern Pharmaceutics, Drugs and the Pharmaceutical Sciences, v. 72, Marcel Dekker, New York, Inc., 1996, herein incorporated by reference.

The C_{max} value is the maximum concentration of the compound achieved in the serum or plasma of a mammal following administration of the compound to the mammal. The C_{max} value of a particular compound can be measured using methods known to those of ordinary skill in the art. The phrases "increasing bioavailability" or "improving the pharmacokinetics," as used herein mean that the systemic availability of a first mmRNA molecule, measured as AUC, C_{max}, or C_{min} in a mammal is greater, when co-administered with a delivery agent as described herein, than when such co-administration does not take place. In some embodiments, the bioavailability of the mmRNA molecule can increase by at least about 2%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100%.

Therapeutic Window

The mmRNA molecules, when formulated into a composition as described herein, can exhibit an increase in the therapeutic window of the administered mmRNA molecule composition as compared to the therapeutic window of the administered mmRNA molecule composition lacking a delivery agent as described herein. As used herein "therapeutic window" refers to the range of plasma concentrations, or the range of levels of therapeutically active substance at the site of action, with a high probability of eliciting a therapeutic effect. In some embodiments, the therapeutic window of the mmRNA molecule when co-administered with a delivery agent as described herein can increase by at least about 2%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100%.

Volume of Distribution

The mmRNA molecules, when formulated into a composition as described herein, can exhibit an improved volume of distribution (V_{dist}). The volume of distribution (V_{dist}) relates the amount of the drug in the body to the concentration of the drug in the blood or plasma. As used herein, the term "volume of distribution" refers to the fluid volume that would be required to contain the total amount of the drug in the body at the same concentration as in the blood or plasma: V_{dist} equals the amount of drug in the body/concentration of drug in blood or plasma. For example, for a 10 mg dose and a plasma concentration of 10 mg/L, the volume of distribution would be 1 liter. The volume of distribution reflects the extent to which the drug is present in the extravascular tissue. A large volume of distribution reflects the tendency of a compound to bind to the tissue components compared with plasma protein binding. In a clinical setting, V_{dist} can be used to determine a loading dose to achieve a steady state concentration. In some embodiments, the volume of distribution of the mmRNA molecule when co-administered with a delivery agent as described herein can decrease at least about 2%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%.

Devices and Methods for Multi-Administration

Methods and devices for multi-administration may be employed to deliver the mmRNA of the present invention according to the split dosing regimens taught herein. Such methods and devices are described below.

Method and devices known in the art for multi-administration to cells, organs and tissues are contemplated for use in conjunction with the methods and compositions disclosed herein as embodiments of the present invention. These include, for example, those methods and devices having multiple needles, hybrid devices employing for example lumens or catheters as well as devices utilizing heat, electric current or radiation driven mechanisms.

According to the present invention, these multi-administration devices may be utilized to deliver the split doses contemplated herein.

Suitable devices for use in delivering intradermal pharmaceutical compositions described herein include short needle devices such as those described in U.S. Pat. Nos. 4,886,499; 5,190,521; 5,328,483; 5,527,288; 4,270,537; 5,015,235; 5,141,496; and 5,417,662. Intradermal compositions may be administered by devices which limit the effective penetration length of a needle into the skin, such as those described in PCT publication WO 99/34850 and functional equivalents thereof. Jet injection devices which

deliver liquid compositions to the dermis via a liquid jet injector and/or via a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Jet injection devices are described, for example, in U.S. Pat. Nos. 5,480,381; 5,599,302; 5,334,144; 5,993,412; 5,649,912; 5,569,189; 5,704,911; 5,383,851; 5,893,397; 5,466,220; 5,339,163; 5,312,335; 5,503,627; 5,064,413; 5,520,639; 4,596,556; 4,790,824; 4,941,880; 4,940,460; and PCT publications WO 97/37705 and WO 97/13537. Ballistic powder/particle delivery devices which use compressed gas to accelerate vaccine in powder form through the outer layers of the skin to the dermis are suitable. Alternatively or additionally, conventional syringes may be used in the classical mantoux method of intradermal administration.

A method for delivering therapeutic agents to a solid tissue has been described by Bahrami et al and is taught for example in US Patent Publication 20110230839, the contents of which are incorporated herein by reference in their entirety. According to Bahrami, an array of needles is incorporated into a device which delivers a substantially equal amount of fluid at any location in said solid tissue along each needle's length.

A device for delivery of biological material across the biological tissue has been described by Kodgule et al and is taught for example in US Patent Publication 20110172610, the contents of which are incorporated herein by reference in their entirety. According to Kodgule, multiple hollow microneedles made of one or more metals and having outer diameters from about 200 microns to about 350 microns and lengths of at least 100 microns are incorporated into the device which delivers peptides, proteins, carbohydrates, nucleic acid molecules, lipids and other pharmaceutically active ingredients or combinations thereof.

A delivery probe for delivering a therapeutic agent to a tissue has been described by Gunday et al and is taught for example in US Patent Publication 20110270184, the contents of which are incorporated herein by reference in their entirety. According to Gunday, multiple needles are incorporated into the device which moves the attached capsules between an activated position and an inactivated position to force the agent out of the capsules through the needles.

A multiple-injection medical apparatus has been described by Assaf and is taught for example in US Patent Publication 20110218497, the contents of which are incorporated herein by reference in their entirety. According to Assaf, multiple needles are incorporated into the device which has a chamber connected to one or more of said needles and a means for continuously refilling the chamber with the medical fluid after each injection.

An at least partially implantable system for injecting a substance into a patient's body, in particular a penis erection stimulation system has been described by Forsell and is taught for example in US Patent Publication 20110196198, the contents of which are incorporated herein by reference in their entirety. According to Forsell, multiple needles are incorporated into the device which is implanted along with one or more housings adjacent the patient's left and right corpora cavernosa. A reservoir and a pump are also implanted to supply drugs through the needles.

A method for the transdermal delivery of a therapeutic effective amount of iron has been described by Berenson and is taught for example in US Patent Publication 20100130910, the contents of which are incorporated herein by reference in their entirety. According to Berenson, multiple needles may be used to create multiple micro channels in stratum corneum to enhance transdermal delivery of the ionic iron on an iontophoretic patch.

A method for delivery of biological material across the biological tissue has been described by Kodgule et al and is taught for example in US Patent Publication 20110196308, the contents of which are incorporated herein by reference in their entirety. According to Kodgule, multiple biodegradable microneedles containing a therapeutic active ingredient are incorporated in a device which delivers proteins, carbohydrates, nucleic acid molecules, lipids and other pharmaceutically active ingredients or combinations thereof.

A transdermal patch comprising a botulinum toxin composition has been described by Donovan and is taught for example in US Patent Publication 20080220020, the contents of which are incorporated herein by reference in their entirety. According to Donovan, multiple needles are incorporated into the patch which delivers botulinum toxin under stratum corneum through said needles which project through the stratum corneum of the skin without rupturing a blood vessel.

A cryoprobe for administration of an active agent to a location of cryogenic treatment has been described by Toubia and is taught for example in US Patent Publication 20080140061, the contents of which are incorporated herein by reference in their entirety. According to Toubia, multiple needles are incorporated into the probe which receives the active agent into a chamber and administers the agent to the tissue.

A method for treating or preventing inflammation or promoting healthy joints has been described by Stock et al and is taught for example in US Patent Publication 20090155186, the contents of which are incorporated herein by reference in their entirety. According to Stock, multiple needles are incorporated in a device which administers compositions containing signal transduction modulator compounds.

A multi-site injection system has been described by Kimmell et al and is taught for example in US Patent Publication 20100256594, the contents of which are incorporated herein by reference in their entirety. According to Kimmell, multiple needles are incorporated into a device which delivers a medication into a stratum corneum through the needles.

A method for delivering interferons to the intradermal compartment has been described by Dekker et al and is taught for example in US Patent Publication 20050181033, the contents of which are incorporated herein by reference in their entirety. According to Dekker, multiple needles having an outlet with an exposed height between 0 and 1 mm are incorporated into a device which improves pharmacokinetics and bioavailability by delivering the substance at a depth between 0.3 mm and 2 mm.

A method for delivering genes, enzymes and biological agents to tissue cells has described by Desai and is taught for example in US Patent Publication 20030073908, the contents of which are incorporated herein by reference in their entirety. According to Desai, multiple needles are incorporated into a device which is inserted into a body and delivers a medication fluid through said needles.

A method for treating cardiac arrhythmias with fibroblast cells has been described by Lee et al and is taught for example in US Patent Publication 20040005295, the contents of which are incorporated herein by reference in their entirety. According to Lee, multiple needles are incorporated into the device which delivers fibroblast cells into the local region of the tissue.

A method using a magnetically controlled pump for treating a brain tumor has been described by Shachar et al and is taught for example in U.S. Pat. No. 7,799,012

(method) and U.S. Pat. No. 7,799,016 (device), the contents of which are incorporated herein by reference in their entirety. According Shachar, multiple needles were incorporated into the pump which pushes a medicating agent through the needles at a controlled rate.

Methods of treating functional disorders of the bladder in mammalian females have been described by Versi et al and are taught for example in U.S. Pat. No. 8,029,496, the contents of which are incorporated herein by reference in their entirety. According to Versi, an array of micro-needles is incorporated into a device which delivers a therapeutic agent through the needles directly into the trigone of the bladder.

A micro-needle transdermal transport device has been described by Angel et al and is taught for example in U.S. Pat. No. 7,364,568, the contents of which are incorporated herein by reference in their entirety. According to Angel, multiple needles are incorporated into the device which transports a substance into a body surface through the needles which are inserted into the surface from different directions.

A device for subcutaneous infusion has been described by Dalton et al and is taught for example in U.S. Pat. No. 7,150,726, the contents of which are incorporated herein by reference in their entirety. According to Dalton, multiple needles are incorporated into the device which delivers fluid through the needles into a subcutaneous tissue.

A device and a method for intradermal delivery of vaccines and gene therapeutic agents through microcannula have been described by Mikszta et al and are taught for example in U.S. Pat. No. 7,473,247, the contents of which are incorporated herein by reference in their entirety. According to Mitszta, at least one hollow micro-needle is incorporated into the device which delivers the vaccines to the subject's skin to a depth of between 0.025 mm and 2 mm.

A method of delivering insulin has been described by Pettis et al and is taught for example in U.S. Pat. No. 7,722,595, the contents of which are incorporated herein by reference in their entirety. According to Pettis, two needles are incorporated into a device wherein both needles insert essentially simultaneously into the skin with the first at a depth of less than 2.5 mm to deliver insulin to intradermal compartment and the second at a depth of greater than 2.5 mm and less than 5.0 mm to deliver insulin to subcutaneous compartment.

Cutaneous injection delivery under suction has been described by Kochamba et al and is taught for example in U.S. Pat. No. 6,896,666, the contents of which are incorporated herein by reference in their entirety. According to Kochamba, multiple needles in relative adjacency with each other are incorporated into a device which injects a fluid below the cutaneous layer.

A device for withdrawing or delivering a substance through the skin has been described by Down et al and is taught for example in U.S. Pat. No. 6,607,513, the contents of which are incorporated herein by reference in their entirety. According to Down, multiple skin penetrating members which are incorporated into the device have lengths of about 100 microns to about 2000 microns and are about 30 to 50 gauge.

A device for delivering a substance to the skin has been described by Palmer et al and is taught for example in U.S. Pat. No. 6,537,242, the contents of which are incorporated herein by reference in their entirety. According to Palmer, an array of micro-needles is incorporated into the device which uses a stretching assembly to enhance the contact of the needles with the skin and provides a more uniform delivery of the substance.

A perfusion device for localized drug delivery has been described by Zamoyski and is taught for example in U.S. Pat. No. 6,468,247, the contents of which are incorporated herein by reference in their entirety. According to Zamoyski, multiple hypodermic needles are incorporated into the device which injects the contents of the hypodermics into a tissue as said hypodermics are being retracted.

A method for enhanced transport of drugs and biological molecules across tissue by improving the interaction between micro-needles and human skin has been described by Prausnitz et al and is taught for example in U.S. Pat. No. 6,743,211, the contents of which are incorporated herein by reference in their entirety. According to Prausnitz, multiple micro-needles are incorporated into a device which is able to present a more rigid and less deformable surface to which the micro-needles are applied.

A device for intraorgan administration of medicinal agents has been described by Ting et al and is taught for example in U.S. Pat. No. 6,077,251, the contents of which are incorporated herein by reference in their entirety. According to Ting, multiple needles having side openings for enhanced administration are incorporated into a device which by extending and retracting said needles from and into the needle chamber forces a medicinal agent from a reservoir into said needles and injects said medicinal agent into a target organ.

A multiple needle holder and a subcutaneous multiple channel infusion port has been described by Brown and is taught for example in U.S. Pat. No. 4,695,273, the contents of which are incorporated herein by reference in their entirety. According to Brown, multiple needles on the needle holder are inserted through the septum of the infusion port and communicate with isolated chambers in said infusion port.

A dual hypodermic syringe has been described by Horn and is taught for example in U.S. Pat. No. 3,552,394, the contents of which are incorporated herein by reference in their entirety. According to Horn, two needles incorporated into the device are spaced apart less than 68 mm and may be of different styles and lengths, thus enabling injections to be made to different depths.

A syringe with multiple needles and multiple fluid compartments has been described by Hershberg and is taught for example in U.S. Pat. No. 3,572,336, the contents of which are incorporated herein by reference in their entirety. According to Hershberg, multiple needles are incorporated into the syringe which has multiple fluid compartments and is capable of simultaneously administering incompatible drugs which are not able to be mixed for one injection.

A surgical instrument for intradermal injection of fluids has been described by Eliscu et al and is taught for example in U.S. Pat. No. 2,588,623, the contents of which are incorporated herein by reference in their entirety. According to Eliscu, multiple needles are incorporated into the instrument which injects fluids intradermally with a wider disperse.

An apparatus for simultaneous delivery of a substance to multiple breast milk ducts has been described by Hung and is taught for example in EP 1818017, the contents of which are incorporated herein by reference in their entirety. According to Hung, multiple lumens are incorporated into the device which inserts though the orifices of the ductal networks and delivers a fluid to the ductal networks.

A catheter for introduction of medications to the tissue of a heart or other organs has been described by Tkebuchava and is taught for example in WO2006138109, the contents of which are incorporated herein by reference in their entirety. According to Tkebuchava, two curved needles are incorporated which enter the organ wall in a flattened trajectory.

Devices for delivering medical agents have been described by Mckay et al and are taught for example in WO2006118804, the content of which are incorporated herein by reference in their entirety. According to Mckay, multiple needles with multiple orifices on each needle are incorporated into the devices to facilitate regional delivery to a tissue, such as the interior disc space of a spinal disc.

A method for directly delivering an immunomodulatory substance into an intradermal space within a mammalian skin has been described by Pettis and is taught for example in WO2004020014, the contents of which are incorporated herein by reference in their entirety. According to Pettis, multiple needles are incorporated into a device which delivers the substance through the needles to a depth between 0.3 mm and 2 mm.

Methods and devices for administration of substances into at least two compartments in skin for systemic absorption and improved pharmacokinetics have been described by Pettis et al and are taught for example in WO2003094995, the contents of which are incorporated herein by reference in their entirety. According to Pettis, multiple needles having lengths between about 300 um and about 5 mm are incorporated into a device which delivers to intradermal and subcutaneous tissue compartments simultaneously.

A drug delivery device with needles and a roller has been described by Zimmerman et al and is taught for example in WO2012006259, the contents of which are incorporated herein by reference in their entirety. According to Zimmerman, multiple hollow needles positioned in a roller are incorporated into the device which delivers the content in a reservoir through the needles as the roller rotates.

Methods and Devices Utilizing Catheters and/or Lumens

Methods and devices using catheters and lumens may be employed to administer the mmRNA of the present invention on a split dosing schedule. Such methods and devices are described below.

A catheter-based delivery of skeletal myoblasts to the myocardium of damaged hearts has been described by Jacoby et al and is taught for example in US Patent Publication 20060263338, the contents of which are incorporated herein by reference in their entirety. According to Jacoby, multiple needles are incorporated into the device at least part of which is inserted into a blood vessel and delivers the cell composition through the needles into the localized region of the subject's heart.

An apparatus for treating asthma using neurotoxin has been described by Deem et al and is taught for example in US Patent Publication 20060225742, the contents of which are incorporated herein by reference in their entirety. According to Deem, multiple needles are incorporated into the device which delivers neurotoxin through the needles into the bronchial tissue.

A method for administering multiple-component therapies has been described by Nayak and is taught for example in U.S. Pat. No. 7,699,803, the contents of which are incorporated herein by reference in their entirety. According to Nayak, multiple injection cannulas may be incorporated into a device wherein depth slots may be included for controlling the depth at which the therapeutic substance is delivered within the tissue.

A surgical device for ablating a channel and delivering at least one therapeutic agent into a desired region of the tissue has been described by McIntyre et al and is taught for example in U.S. Pat. No. 8,012,096, the contents of which are incorporated herein by reference in their entirety. According to McIntyre, multiple needles are incorporated into the device which dispenses a therapeutic agent into a region of tissue surrounding the channel and is particularly well suited for transmyocardial revascularization operations.

Methods of treating functional disorders of the bladder in mammalian females have been described by Versi et al and are taught for example in U.S. Pat. No. 8,029,496, the contents of which are incorporated herein by reference in their entirety. According to Versi, an array of micro-needles is incorporated into a device which delivers a therapeutic agent through the needles directly into the trigone of the bladder.

A device and a method for delivering fluid into a flexible biological barrier have been described by Yeshurun et al and are taught for example in U.S. Pat. No. 7,998,119 (device) and U.S. Pat. No. 8,007,466 (method), the contents of which are incorporated herein by reference in their entirety. According to Yeshurun, the micro-needles on the device penetrate and extend into the flexible biological barrier and fluid is injected through the bore of the hollow micro-needles.

A method for epicardially injecting a substance into an area of tissue of a heart having an epicardial surface and disposed within a torso has been described by Bonner et al and is taught for example in U.S. Pat. No. 7,628,780, the contents of which are incorporated herein by reference in their entirety. According to Bonner, the devices have elongate shafts and distal injection heads for driving needles into tissue and injecting medical agents into the tissue through the needles.

A device for sealing a puncture has been described by Nielsen et al and is taught for example in U.S. Pat. No. 7,972,358, the contents of which are incorporated herein by reference in their entirety. According to Nielsen, multiple needles are incorporated into the device which delivers a closure agent into the tissue surrounding the puncture tract.

A method for myogenesis and angiogenesis has been described by Chiu et al and is taught for example in U.S. Pat. No. 6,551,338, the contents of which are incorporated herein by reference in their entirety. According to Chiu, 5 to 15 needles having a maximum diameter of at least 1.25 mm and a length effective to provide a puncture depth of 6 to 20 mm are incorporated into a device which inserts into proximity with a myocardium and supplies an exogeneous angiogenic or myogenic factor to said myocardium through the conduits which are in at least some of said needles.

A method for the treatment of prostate tissue has been described by Bolmsj et al and is taught for example in U.S. Pat. No. 6,524,270, the contents of which are incorporated herein by reference in their entirety. According to Bolmsj, a device comprising a catheter which is inserted through the urethra has at least one hollow tip extendible into the surrounding prostate tissue. An astringent and analgesic medicine is administered through said tip into said prostate tissue.

A method for infusing fluids to an intraosseous site has been described by Findlay et al and is taught for example in U.S. Pat. No. 6,761,726, the contents of which are incorporated herein by reference in their entirety. According to Findlay, multiple needles are incorporated into a device which is capable of penetrating a hard shell of material

covered by a layer of soft material and delivers a fluid at a predetermined distance below said hard shell of material.

A device for injecting medications into a vessel wall has been described by Vigil et al and is taught for example in U.S. Pat. No. 5,713,863, the contents of which are incorporated herein by reference in their entirety. According to Vigil, multiple injectors are mounted on each of the flexible tubes in the device which introduces a medication fluid through a multi-lumen catheter, into said flexible tubes and out of said injectors for infusion into the vessel wall.

A catheter for delivering therapeutic and/or diagnostic agents to the tissue surrounding a bodily passageway has been described by Faxon et al and is taught for example in U.S. Pat. No. 5,464,395, the contents of which are incorporated herein by reference in their entirety. According to Faxon, at least one needle cannula is incorporated into the catheter which delivers the desired agents to the tissue through said needles which project outboard of the catheter.

Balloon catheters for delivering therapeutic agents have been described by Orr and are taught for example in WO2010024871, the contents of which are incorporated herein by reference in their entirety. According to Orr, multiple needles are incorporated into the devices which deliver the therapeutic agents to different depths within the tissue.

Methods and Devices Utilizing Electrical Current

Methods and devices utilizing electric current may be employed to deliver the mmRNA of the present invention according to the split dosing regimens taught herein. Such methods and devices are described below.

An electro collagen induction therapy device has been described by Marquez and is taught for example in US Patent Publication 20090137945, the contents of which are incorporated herein by reference in their entirety. According to Marquez, multiple needles are incorporated into the device which repeatedly pierce the skin and draw in the skin a portion of the substance which is applied to the skin first.

An electrokinetic system has been described by Etheredge et al and is taught for example in US Patent Publication 20070185432, the contents of which are incorporated herein by reference in their entirety. According to Etheredge, micro-needles are incorporated into a device which drives by an electrical current the medication through the needles into the targeted treatment site.

An iontophoresis device has been described by Matsumura et al and is taught for example in U.S. Pat. No. 7,437,189, the contents of which are incorporated herein by reference in their entirety. According to Matsumura, multiple needles are incorporated into the device which is capable of delivering ionizable drug into a living body at higher speed or with higher efficiency.

Intradermal delivery of biologically active agents by needle-free injection and electroporation has been described by Hoffmann et al and is taught for example in U.S. Pat. No. 7,171,264, the contents of which are incorporated herein by reference in their entirety. According to Hoffmann, one or more needle-free injectors are incorporated into an electroporation device and the combination of needle-free injection and electroporation is sufficient to introduce the agent into cells in skin, muscle or mucosa.

A method for electropermeabilization-mediated intracellular delivery has been described by Lundkvist et al and is taught for example in U.S. Pat. No. 6,625,486, the contents of which are incorporated herein by reference in their entirety. According to Lundkvist, a pair of needle electrodes is incorporated into a catheter. Said catheter is positioned into a body lumen followed by extending said needle electrodes to penetrate into the tissue surrounding said lumen. Then the device introduces an agent through at least one of said needle electrodes and applies electric field by said pair of needle electrodes to allow said agent pass through the cell membranes into the cells at the treatment site.

A delivery system for transdermal immunization has been described by Levin et al and is taught for example in WO2006003659, the contents of which are incorporated herein by reference in their entirety. According to Levin, multiple electrodes are incorporated into the device which applies electrical energy between the electrodes to generate micro channels in the skin to facilitate transdermal delivery.

A method for delivering RF energy into skin has been described by Schomacker and is taught for example in WO2011163264, the contents of which are incorporated herein by reference in their entirety. According to Schomacker, multiple needles are incorporated into a device which applies vacuum to draw skin into contact with a plate so that needles insert into skin through the holes on the plate and deliver RF energy.

Devices and Kits

Devices may also be used in conjunction with the present invention. In one embodiment, a device is used to assess levels of a protein which has been administered in the form of a modified mRNA. The device may comprise a blood, urine or other biofluidic test. It may be as large as to include an automated central lab platform or a small decentralized bench top device. It may be point of care or a handheld device. The device may be useful in drug discovery efforts as a companion diagnostic.

In some embodiments the device is self-contained, and is optionally capable of wireless remote access to obtain instructions for synthesis and/or analysis of the generated nucleic acid. The device is capable of mobile synthesis of at least one nucleic acid, and preferably an unlimited number of different nucleic acid sequences. In certain embodiments, the device is capable of being transported by one or a small number of individuals. In other embodiments, the device is scaled to fit on a benchtop or desk. In other embodiments, the device is scaled to fit into a suitcase, backpack or similarly sized object. In further embodiments, the device is scaled to fit into a vehicle, such as a car, truck or ambulance, or a military vehicle such as a tank or personnel carrier. The information necessary to generate a modified mRNA encoding protein of interest is present within a computer readable medium present in the device.

In some embodiments, the device is capable of communication (e.g., wireless communication) with a database of nucleic acid and polypeptide sequences. The device contains at least one sample block for insertion of one or more sample vessels. Such sample vessels are capable of accepting in liquid or other form any number of materials such as template DNA, nucleotides, enzymes, buffers, and other reagents. The sample vessels are also capable of being heated and cooled by contact with the sample block. The sample block is generally in communication with a device base with one or more electronic control units for the at least one sample block. The sample block preferably contains a heating module, such heating molecule capable of heating and/or cooling the sample vessels and contents thereof to temperatures between about −20 C and above +100 C. The device base is in communication with a voltage supply such as a battery or external voltage supply. The device also contains means for storing and distributing the materials for RNA synthesis.

Optionally, the sample block contains a module for separating the synthesized nucleic acids. Alternatively, the device contains a separation module operably linked to the sample block. Preferably the device contains a means for analysis of the synthesized nucleic acid. Such analysis includes sequence identity (demonstrated such as by hybridization), absence of non-desired sequences, measurement of integrity of synthesized mRNA (such has by microfluidic viscometry combined with spectrophotometry), and concentration and/orpotency of modified RNA (such as by spectrophotometry).

In certain embodiments, the device is combined with a means for detection of pathogens present in a biological material obtained from a subject, e.g., the IBIS PLEX-ID system (Abbott) for microbial identification.

The present invention provides for devices which incorporate mmRNA that encode proteins of interest. These devices may be implantable in an animal subject or may supply mmRNA formulations via a catheter or lumen. The device may be connected to or incorporate a pump. Such devices include those which can deliver therapeutics to areas of the body not readily accessible such as the CNS or across the blood brain barrier. In this embodiment the split dosing regimen can be implemented using a regulated pump.

Kits

The invention provides a variety of kits for conveniently and/or effectively carrying out methods of the present invention. Typically kits will comprise sufficient amounts and/or numbers of components to allow a user to perform multiple treatments of a subject(s) and/or to perform multiple experiments.

In one aspect, the present invention provides kits for protein production, comprising a first isolated nucleic acid comprising a translatable region and a nucleic acid modification, wherein the nucleic acid may be capable of evading an innate immune response of a cell into which the first isolated nucleic acid may be introduced, and packaging and instructions. The kit may further comprise a delivery agent to form a formulation composition. The delivery composition may comprise a lipidoid. The lipoid may be selected from, but is not limited to, C12-200, 98N12-5, MD1, DLin-DMA, DLin-K-DMA, DLin-KC2-DMA, DLin-MC3-DMA and analogs thereof.

In one aspect, the present invention provides kits for protein production, comprising a first isolated nucleic acid comprising a translatable region and a nucleoside modification, wherein the nucleic acid exhibits reduced degradation by a cellular nuclease, and packaging and instructions.

In one aspect, the present invention provides kits for protein production, comprising a first isolated nucleic acid comprising a translatable region and at least two different nucleoside modifications, wherein the nucleic acid exhibits reduced degradation by a cellular nuclease, and packaging and instructions.

In some embodiments, kits would provide split doses or instructions for the administration of split dosages of the mmRNA of the kit.

Definitions

At various places in the present specification, substituents of compounds of the present disclosure are disclosed in groups or in ranges. It is specifically intended that the present disclosure include each and every individual subcombination of the members of such groups and ranges. For example, the term "C_{1-6} alkyl" is specifically intended to individually disclose methyl, ethyl, C_3 alkyl, C_4 alkyl, C_5 alkyl, and C_6 alkyl.

Animal: As used herein, the term "animal" refers to any member of the animal kingdom. In some embodiments, "animal" refers to humans at any stage of development. In some embodiments, "animal" refers to non-human animals at any stage of development. In certain embodiments, the non-human animal is a mammal (e.g., a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate, or a pig). In some embodiments, animals include, but are not limited to, mammals, birds, reptiles, amphibians, fish, and worms. In some embodiments, the animal is a transgenic animal, genetically-engineered animal, or a clone.

Approximately: As used herein, the term "approximately" or "about," as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In certain embodiments, the term "approximately" or "about" refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

Associated with: As used herein, the terms "associated with," "conjugated," "linked," "attached," and "tethered," when used with respect to two or more moieties, means that the moieties are physically associated or connected with one another, either directly or via one or more additional moieties that serves as a linking agent, to form a structure that is sufficiently stable so that the moieties remain physically associated under the conditions in which the structure is used, e.g., physiological conditions. An "association" need not be strictly through direct covalent chemical bonding. It may also suggest ionic or hydrogen bonding or a hybridization based connectivity sufficiently stable such that the "associated" entities remain physically associated.

Bifunctional: As used herein, the term "bifunctional" refers to any substance, molecule or moiety which is capable of or maintains at least two functions. The functions may effect the same outcome or a different outcome. The structure that produces the function may be the same or different. For example, bifunctional modified RNAs of the present invention may encode a cytotoxic peptide (a first function) while those nucleosides which comprise the encoding RNA are, in and of themselves, cytotoxic (second function). In this example, delivery of the bifunctional modified RNA to a cancer cell would produce not only a peptide or protein molecule which may ameliorate or treat the cancer but would also deliver a cytotoxic payload of nucleosides to the cell should degradation, instead of translation of the modified RNA, occur.

Biologically active: As used herein, the phrase "biologically active" refers to a characteristic of any substance that has activity in a biological system and/or organism. For instance, a substance that, when administered to an organism, has a biological affect on that organism, is considered to be biologically active. In particular embodiments, a nucleic acid molecule of the present invention may be considered biologically active if even a portion of the nucleic acid molecule is biologically active or mimics an activity considered biologically relevant.

Chemical terms: As used herein, the term "alkyl" is meant to refer to a saturated hydrocarbon group which is straight-chained or branched. Example alkyl groups include methyl (Me), ethyl (Et), propyl (e.g., n-propyl and isopropyl), butyl

(e.g., n-butyl, isobutyl, t-butyl), pentyl (e.g., n-pentyl, isopentyl, neopentyl), and the like. An alkyl group can contain from 1 to about 20, from 2 to about 20, from 1 to about 12, from 1 to about 8, from 1 to about 6, from 1 to about 4, or from 1 to about 3 carbon atoms.

As used herein, "alkenyl" refers to an alkyl group having one or more double carbon-carbon bonds. Example alkenyl groups include ethenyl, propenyl, and the like.

As used herein, "alkoxy" refers to an —O-alkyl group. Example alkoxy groups include methoxy, ethoxy, propoxy (e.g., n-propoxy and isopropoxy), t-butoxy, and the like.

As used herein, "alkenyl" refers to an alkyl, as defined above, containing at least one double bond between adjacent carbon atoms. Alkenyls include both cis and trans isomers. Representative straight chain and branched alkenyls include ethylenyl, propylenyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, and the like.

As used herein, "alkynyl" refers to an alkyl group having one or more triple carbon-carbon bonds. Example alkynyl groups include ethynyl, propynyl, and the like.

As used herein, "aryl" refers to monocyclic or polycyclic (e.g., having 2, 3 or 4 fused rings) aromatic hydrocarbons such as, for example, phenyl, naphthyl, anthracenyl, phenanthrenyl, indanyl, indenyl, and the like. In some embodiments, aryl groups have from 6 to about 20 carbon atoms.

As used herein, "halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

Compound: As used herein, the term "compound," is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted.

The compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present disclosure that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C═N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present disclosure. Cis and trans geometric isomers of the compounds of the present disclosure are described and may be isolated as a mixture of isomers or as separated isomeric forms.

Compounds of the present disclosure also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond and the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Examples prototropic tautomers include ketone-enol pairs, amide-imidic acid pairs, lactam-lactim pairs, amide-imidic acid pairs, enamine-imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, such as, 1H- and 3H-imidazole, 1H-, 2H- and 4H-1,2,4-triazole, 1H- and 2H-isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

Compounds of the present disclosure also include all of the isotopes of the atoms occurring in the intermediate or final compounds. "Isotopes" refers to atoms having the same atomic number but different mass numbers resulting from a different number of neutrons in the nuclei. For example, isotopes of hydrogen include tritium and deuterium.

The compounds and salts of the present disclosure can be prepared in combination with solvent or water molecules to form solvates and hydrates by routine methods.

Conserved: As used herein, the term "conserved" refers to nucleotides or amino acid residues of a polynucleotide sequence or polypeptide sequence, respectively, that are those that occur unaltered in the same position of two or more sequences being compared. Nucleotides or amino acids that are relatively conserved are those that are conserved amongst more related sequences than nucleotides or amino acids appearing elsewhere in the sequences.

In some embodiments, two or more sequences are said to be "completely conserved" if they are 100% identical to one another. In some embodiments, two or more sequences are said to be "highly conserved" if they are at least 70% identical, at least 80% identical, at least 90% identical, or at least 95% identical to one another. In some embodiments, two or more sequences are said to be "highly conserved" if they are about 70% identical, about 80% identical, about 90% identical, about 95%, about 98%, or about 99% identical to one another. In some embodiments, two or more sequences are said to be "conserved" if they are at least 30% identical, at least 40% identical, at least 50% identical, at least 60% identical, at least 70% identical, at least 80% identical, at least 90% identical, or at least 95% identical to one another. In some embodiments, two or more sequences are said to be "conserved" if they are about 30% identical, about 40% identical, about 50% identical, about 60% identical, about 70% identical, about 80% identical, about 90% identical, about 95% identical, about 98% identical, or about 99% identical to one another. Conservation of sequence may apply to the entire length of an oligonucleotide or polypeptide or may apply to a portion, region or feature thereof.

Delivery: As used herein, "delivery" refers to the act or manner of delivering a compound, substance, entity, moiety, cargo or payload.

Delivery Agent: As used herein, "delivery agent" refers to any substance which facilitates, at least in part, the in vivo delivery of a nucleic acid molecule to targeted cells.

Detectable label: As used herein, "detectable label" refers to one or more markers, signals, or moieties which are attached, incorporated or associated with another entity that is readily detected by methods known in the art including radiography, fluorescence, chemiluminescence, enzymatic activity, absorbance and the like. Detectable labels include radioisotopes, fluorophores, chromophores, enzymes, dyes, metal ions, ligands such as biotin, avidin, strepavidin and haptens, quantum dots, and the like. Detectable labels may be located at any position in the peptides or proteins disclosed herein. They may be within the amino acids, the peptides, or proteins, or located at the N- or C-termini.

Distal: As used herein "distal" means farther from center mass or line of symmetry of subject or reference point. For limbs, it is farther from body.

Dosing regimen: As used herein, a "dosing regimen" is a schedule of administration or physician determined regimen of treatment, prophylaxis, or palliative care.

Dose splitting factor (DSF)-ratio of PUD of dose split treatment divided by PUD of total daily dose or single unit dose. The value is derived from comparison of dosing regimens groups.

Expression: As used herein, "expression" of a nucleic acid sequence refers to one or more of the following events: (1) production of an RNA template from a DNA sequence (e.g., by transcription); (2) processing of an RNA transcript (e.g.,

by splicing, editing, 5' cap formation, and/or 3' end processing); (3) translation of an RNA into a polypeptide or protein; and (4) post-translational modification of a polypeptide or protein.

Formulation: As used herein, a "formulation" includes at least a modified nucleic acid molecule and a delivery agent.

Functional: As used herein, a "functional" biological molecule is a biological molecule in a form in which it exhibits a property and/or activity by which it is characterized.

Homology: As used herein, the term "homology" refers to the overall relatedness between polymeric molecules, e.g. between nucleic acid molecules (e.g. DNA molecules and/or RNA molecules) and/or between polypeptide molecules. In some embodiments, polymeric molecules are considered to be "homologous" to one another if their sequences are at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical. In some embodiments, polymeric molecules are considered to be "homologous" to one another if their sequences are at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% similar. The term "homologous" necessarily refers to a comparison between at least two sequences (polynucleotide or polypeptide sequences).

In accordance with the invention, two polynucleotide sequences are considered to be homologous if the polypeptides they encode are at least about 50% identical, at least about 60% identical, at least about 70% identical, at least about 80% identical, or at least about 90% identical for at least one stretch of at least about 20 amino acids.

In some embodiments, homologous polynucleotide sequences are characterized by the ability to encode a stretch of at least 4-5 uniquely specified amino acids. For polynucleotide sequences less than 60 nucleotides in length, homology is determined by the ability to encode a stretch of at least 4-5 uniquely specified amino acids. In accordance with the invention, two protein sequences are considered to be homologous if the proteins are at least about 50% identical, at least about 60% identical, at least about 70% identical, at least about 80% identical, or at least about 90% identical for at least one stretch of at least about 20 amino acids.

Identity: As used herein, the term "identity" refers to the overall relatedness between polymeric molecules, e.g., between oligonucleotide molecules (e.g. DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of the percent identity of two polynucleotide sequences, for example, can be performed by aligning the two sequences for optimal comparison purposes (e.g., gaps can be introduced in one or both of a first and a second nucleic acid sequences for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or 100% of the length of the reference sequence. The nucleotides at corresponding nucleotide positions are then compared. When a position in the first sequence is occupied by the same nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which needs to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. For example, the percent identity between two nucleotide sequences can be determined using methods such as those described in Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; Computer Analysis of Sequence Data, Part I, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; each of which is incorporated herein by reference. For example, the percent identity between two nucleotide sequences can be determined using the algorithm of Meyers and Miller (CABIOS, 1989, 4:11-17), which has been incorporated into the ALIGN program (version 2.0) using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. The percent identity between two nucleotide sequences can, alternatively, be determined using the GAP program in the GCG software package using an NWSgapdna.CMP matrix. Methods commonly employed to determine percent identity between sequences include, but are not limited to those disclosed in Carillo, H., and Lipman, D., SIAM J Applied Math., 48:1073 (1988); incorporated herein by reference. Techniques for determining identity are codified in publicly available computer programs. Exemplary computer software to determine homology between two sequences include, but are not limited to, GCG program package, Devereux, J., et al., *Nucleic Acids Research,* 12(1), 387 (1984)), BLASTP, BLASTN, and FASTA Atschul, S. F. et al., *J. Molec. Biol.,* 215, 403 (1990)).

Inhibit expression of a gene: As used herein, the phrase "inhibit expression of a gene" means to cause a reduction in the amount of an expression product of the gene. The expression product can be an RNA transcribed from the gene (e.g., an mRNA) or a polypeptide translated from an mRNA transcribed from the gene. Typically a reduction in the level of an mRNA results in a reduction in the level of a polypeptide translated therefrom. The level of expression may be determined using standard techniques for measuring mRNA or protein.

In vitro: As used herein, the term "in vitro" refers to events that occur in an artificial environment, e.g., in a test tube or reaction vessel, in cell culture, in a Petri dish, etc., rather than within an organism (e.g., animal, plant, or microbe).

In vivo: As used herein, the term "in vivo" refers to events that occur within an organism (e.g., animal, plant, or microbe or cell or tissue thereof).

Isolated: As used herein, the term "isolated" refers to a substance or entity that has been separated from at least some of the components with which it was associated (whether in nature or in an experimental setting). Isolated substances may have varying levels of purity in reference to the substances from which they have been associated. Isolated substances and/or entities may be separated from at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or more of the other components with which they were initially associated. In some embodiments, isolated agents are more than about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about

97%, about 98%, about 99%, or more than about 99% pure. As used herein, a substance is "pure" if it is substantially free of other components. Substantially isolated: By "substantially isolated" is meant that the compound is substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in the compound of the present disclosure. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compound of the present disclosure, or salt thereof. Methods for isolating compounds and their salts are routine in the art.

Modified: As used herein "modified" refers to a changed state or structure of a molecule of the invention. Molecules may be modified in many ways including chemically, structurally, and functionally. In one embodiment, the mRNA molecules of the present invention are modified by the introduction of non-natural nucleosides and/or nucleotides. Modified, as it pertains to a modified mRNA may also mean any alteration which is different from the wild type.

Naturally occurring: As used herein, "naturally occurring" means existing in nature without artificial aid.

Patient: As used herein, "patient" refers to a subject who may seek or be in need of treatment, requires treatment, is receiving treatment, will receive treatment, or a subject who is under care by a trained professional for a particular disease or condition.

Peptide: As used herein, "peptide" is less than or equal to 50 amino acids long, e.g., about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acids long.

Prodrug: The present disclosure also includes prodrugs of the compounds described herein. As used herein, "prodrugs" refer to any substance, molecule or entity which is in a form predicate for that substance, molecule or entity to act as a therapeutic upon chemical or physical alteration. Prodrugs may by covalently bonded or sequestested in some way and which release or are converted into the active drug moiety prior to, upon or after administered to a mammalian subject. Prodrugs can be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compounds. Prodrugs include compounds wherein hydroxyl, amino, sulfhydryl, or carboxyl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, sulfhydryl, or carboxyl group respectively. Preparation and use of prodrugs is discussed in T. Higuchi and V. Stella, "Prodrugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are hereby incorporated by reference in their entirety.

Proliferate: As used herein, the term "proliferate" means to grow, expand or increase or cause to grow, expand or increase rapidly. "Proliferative" means having the ability to proliferate. "Anti-proliferative" means having properties counter to or inapposite to proliferative properties.

Pharmaceutically acceptable: The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

Pharmaceutically acceptable salts: The present disclosure also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present disclosure include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present disclosure can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences,* 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and *Journal of Pharmaceutical Science,* 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

Polypeptide: As used herein, "polypeptide" means a polymer of amino acid residues linked together by peptide bonds. The term, as used herein, refers to proteins, polypeptides, and peptides of any size, structure, or function. Typically, however, a polypeptide will be at least 50 amino acids long. In some instances the polypeptide encoded is smaller than about 50 amino acids and the polypeptide is termed a peptide. If the polypeptide is a peptide, it will be at least about 5 amino acid residues long. Thus, polypeptides include gene products, naturally occurring polypeptides, synthetic polypeptides, homologs, orthologs, paralogs, fragments and other equivalents, variants, and analogs of the foregoing. A polypeptide may be a single molecule or may be a multi-molecular complex such as a dimer, trimer or tetramer. The term polypeptide may also apply to amino acid polymers in which one or more amino acid residues are an artificial chemical analogue of a corresponding naturally occurring amino acid.

Polypeptide per unit drug (PUD): As used herein, a PUD or product per unit drug, is defined as a subdivided portion of total daily dose, usually 1 mg, pg, kg, etc., of a product (such as a polypeptide) as measured in body fluid or tissue, usually defined in concentration such as pmol/mL, mmol/mL, etc divided by the measure in the body fluid.

Proximal: As used herein, "proximal" means closer to center mass or line of symmetry of subject or reference point. For limbs, it is closer to body.

Sample: As used herein, the term "sample" refers to a subset of its tissues, cells or component parts (e.g. body fluids, including but not limited to peripheral blood, serum, plasma, ascites, urine, cerebrospinal fluid (CSF), sputum, saliva, bone marrow, synovial fluid, aqueous humor, amniotic fluid, cerumen, breast milk, broncheoalveolar lavage fluid, semen, prostatic fluid, cowper's fluid or pre-ejaculatory fluid, sweat, fecal matter, hair, tears, cyst fluid, pleural and peritoneal fluid, pericardial fluid, lymph, chyme, chyle, bile, interstitial fluid, menses, pus, sebum, vomit, vaginal secretions, mucosal secretion, stool water, pancreatic juice, lavage fluids from sinus cavities, bronchopulmonary aspirates, blastocyl cavity fluid, and umbilical cord blood). A

sample further may include a homogenate, lysate or extract prepared from a whole organism or a subset of its tissues, cells or component parts, or a fraction or portion thereof, including but not limited to, for example, plasma, serum, spinal fluid, lymph fluid, the external sections of the skin, respiratory, intestinal, and genitourinary tracts, tears, saliva, milk, blood cells, tumors, organs. A sample further refers to a medium, such as a nutrient broth or gel, which may contain cellular components, such as proteins or nucleic acid molecule.

Similarity: As used herein, the term "similarity" refers to the overall relatedness between polymeric molecules, e.g. between polynucleotide molecules (e.g. DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of percent similarity of polymeric molecules to one another can be performed in the same manner as a calculation of percent identity, except that calculation of percent similarity takes into account conservative substitutions as is understood in the art.

Stable: As used herein "stable" refers to a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and preferably capable of formulation into an efficacious therapeutic agent.

Subject: As used herein, the term "subject" or "patient" refers to any organism to which a composition in accordance with the invention may be administered, e.g., for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Typical subjects include animals (e.g., mammals such as mice, rats, rabbits, non-human primates, and humans) and/or plants.

Substantially: As used herein, the term "substantially" refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the biological arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term "substantially" is therefore used herein to capture the potential lack of completeness inherent in many biological and chemical phenomena.

Substantially equal: As used herein as it relates to time differences between doses, the term means plus/minus 2%.

Substantially simultaneously: As used herein and as it relates to plurality of doses, the term means within 2 seconds.

Simultaneously: As used herein, "simultaneously" means within scientific reproducibility, at same time.

Suffering from: An individual who is "suffering from" a disease, disorder, and/or condition has been diagnosed with or displays one or more symptoms of a disease, disorder, and/or condition.

Susceptible to: An individual who is "susceptible to" a disease, disorder, and/or condition has not been diagnosed with and/or may not exhibit symptoms of the disease, disorder, and/or condition but harbors a propensity to develop a disease or its symptoms. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition (for example, cancer) may be characterized by one or more of the following: (1) a genetic mutation associated with development of the disease, disorder, and/or condition; (2) a genetic polymorphism associated with development of the disease, disorder, and/or condition; (3) increased and/or decreased expression and/or activity of a protein and/or nucleic acid associated with the disease, disorder, and/or condition; (4) habits and/or lifestyles associated with development of the disease, disorder, and/or condition; (5) a family history of the disease, disorder, and/or condition; and (6) exposure to and/or infection with a microbe associated with development of the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will develop the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will not develop the disease, disorder, and/or condition.

Synthetic: The term "synthetic" means produced, prepared, and/or manufactured by the hand of man. Synthesis of polynucleotides or polypeptides or other molecules of the present invention may be chemical or enzymatic.

Single unit dose: As used herein, a "single unit dose" is a dose of any therapeutic administered in one dose/at one time/single route/single point of contact, i.e., single administration event.

Total daily dose: As used herein, a "total daily dose" is an amount given or prescribed in 24 hr period. It may be administered as a single unit dose.

Split dose: As used herein, a "split dose" is the division of single unit dose or total daily dose into two or more doses.

Targeted Cells: As used herein, "targeted cells" refers to any one or more cells of interest. The cells may be found in vitro, in vivo, in situ or in the tissue or organ of an organism. The organism may be an animal, preferably a mammal, more preferably a human and most preferably a patient.

Therapeutic Agent: The term "therapeutic agent" refers to any agent that, when administered to a subject, has a therapeutic, diagnostic, and/or prophylactic effect and/or elicits a desired biological and/or pharmacological effect.

Therapeutically effective amount: As used herein, the term "therapeutically effective amount" means an amount of an agent to be delivered (e.g., nucleic acid, drug, therapeutic agent, diagnostic agent, prophylactic agent, etc.) that is sufficient, when administered to a subject suffering from or susceptible to a disease, disorder, and/or condition, to treat, improve symptoms of, diagnose, prevent, and/or delay the onset of the disease, disorder, and/or condition.

Transcription factor: As used herein, the term "transcription factor" refers to a DNA-binding protein that regulates transcription of DNA into RNA, for example, by activation or repression of transcription. Some transcription factors effect regulation of transcription alone, while others act in concert with other proteins. Some transcription factor can both activate and repress transcription under certain conditions. In general, transcription factors bind a specific target sequence or sequences highly similar to a specific consensus sequence in a regulatory region of a target gene. Transcription factors may regulate transcription of a target gene alone or in a complex with other molecules.

Treating: As used herein, the term "treating" refers to partially or completely alleviating, ameliorating, improving, relieving, delaying onset of, inhibiting progression of, reducing severity of, and/or reducing incidence of one or more symptoms or features of a particular disease, disorder, and/or condition. For example, "treating" cancer may refer to inhibiting survival, growth, and/or spread of a tumor. Treatment may be administered to a subject who does not exhibit signs of a disease, disorder, and/or condition and/or to a subject who exhibits only early signs of a disease, disorder, and/or condition for the purpose of decreasing the risk of developing pathology associated with the disease, disorder, and/or condition.

Unmodified: As used herein, "unmodified" refers to any substance, compound or molecule prior to being changed in any way. Unmodified may, but does not always, refer to the wild type or native form of a biomolecule. Molecules may

undergo a series of modifications whereby each modified molecule may serve as the "unmodified" starting molecule for a subsequent modification.

Equivalents and Scope

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments in accordance with the invention described herein. The scope of the present invention is not intended to be limited to the above Description, but rather is as set forth in the appended claims.

In the claims, articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

It is also noted that the term "comprising" is intended to be open and permits the inclusion of additional elements or steps.

Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or subrange within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

In addition, it is to be understood that any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Since such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the compositions of the invention (e.g., any nucleic acid or protein encoded thereby; any method of production; any method of use; etc.) can be excluded from any one or more claims, for any reason, whether or not related to the existence of prior art.

As used herein and in the claims, the singular forms include the plural reference and vice versa unless the context clearly indicates otherwise. Other than in the operating examples, or where otherwise indicated, all numbers expressing quantities of ingredients or reaction conditions used herein should be understood as modified in all instances by the term "about."

All patents, oligonucleotide sequences identified by gene identification numbers, and other publications identified herein are expressly incorporated by reference for the purpose of describing and disclosing, for example, the methodologies described in such publications that might be used in connection with the present invention. These publications are provided solely for their disclosure prior to the filing date of the present application. Nothing in this regard should be construed as an admission that the inventors are not entitled to antedate such disclosure by virtue of prior invention or for any other reason. All statements as to the date or representation as to the contents of these documents is based on the information available to the applicants and does not constitute any admission as to the correctness of the dates or contents of these documents.

All cited sources, for example, references, publications, databases, database entries, and art cited herein, are incorporated into this application by reference, even if not expressly stated in the citation. In case of conflicting statements of a cited source and the instant application, the statement in the instant application shall control.

EXAMPLES

Example 1. Modified mRNA Production

Modified mRNAs (mmRNA) according to the invention may be made using standard laboratory methods and materials. The open reading frame (ORF) of the gene of interest may be flanked by a 5' untranslated region (UTR) which may contain a strong Kozak translational initiation signal and/or an alpha-globin 3' UTR which may include an oligo(dT) sequence for templated addition of a poly-A tail. The modified mRNAs may be modified to reduce the cellular innate immune response. The modifications to reduce the cellular response may include pseudouridine (ψ) and 5-methylcytidine (5meC or m^5C). (see, Kariko K et al. Immunity 23:165-75 (2005), Kariko K et al. Mol Ther 16:1833-40 (2008), Anderson B R et al. NAR (2010); herein incorporated by reference).

The ORF may also include various upstream or downstream additions (such as, but not limited to, β-globin, tags, etc.) may be ordered from an optimization service such as, but limited to, DNA2.0 (Menlo Park, Calif.) and may contain multiple cloning sites which may have XbaI recognition. Upon receipt of the construct, it may be reconstituted and transformed into chemically competent *E. coli.*

For the present invention, NEB DH5-alpha Competent *E. coli* are used. Transformations are performed according to NEB instructions using 100 ng of plasmid. The protocol is as follows:

1. Thaw a tube of NEB 5-alpha Competent *E. coli* cells on ice for 10 minutes.
2. Add 1-5 μl containing 1 pg-100 ng of plasmid DNA to the cell mixture. Carefully flick the tube 4-5 times to mix cells and DNA. Do not vortex.
3. Place the mixture on ice for 30 minutes. Do not mix.
4. Heat shock at 42° C. for exactly 30 seconds. Do not mix.
5. Place on ice for 5 minutes. Do not mix.
6. Pipette 950 μl of room temperature SOC into the mixture.
7. Place at 37° C. for 60 minutes. Shake vigorously (250 rpm) or rotate.
8. Warm selection plates to 37° C.
9. Mix the cells thoroughly by flicking the tube and inverting.
10. Spread 50-100 μl of each dilution onto a selection plate and incubate overnight at 37° C. Alternatively, incubate at 30° C. for 24-36 hours or 25° C. for 48 hours.

A single colony is then used to inoculate 5 ml of LB growth media using the appropriate antibiotic and then allowed to grow (250 RPM, 37° C.) for 5 hours. This is then used to inoculate a 200 ml culture medium and allowed to grow overnight under the same conditions.

To isolate the plasmid (up to 850 μg), a maxi prep is performed using the Invitrogen PURELINK™ HiPure Maxiprep Kit (Carlsbad, Calif.), following the manufacturer's instructions.

In order to generate cDNA for In Vitro Transcription (IVT), the plasmid (an Example of which is shown in FIG. **2**) is first linearized using a restriction enzyme such as XbaI. A typical restriction digest with XbaI will comprise the following: Plasmid 1.0 μg; 10× Buffer 1.0 μl; XbaI 1.5 μl; dH_2O up to 10 μl; incubated at 37° C. for 1 hr. If performing at lab scale (<5 μg), the reaction is cleaned up using Invitrogen's PURELINK™ PCR Micro Kit (Carlsbad, Calif.) per manufacturer's instructions. Larger scale purifications may need to be done with a product that has a larger load capacity such as Invitrogen's standard PURELINK™ PCR Kit (Carlsbad, Calif.). Following the cleanup, the linearized vector is quantified using the NanoDrop and analyzed to confirm linearization using agarose gel electrophoresis.

As a non-limiting example, G-CSF may represent the polypeptide of interest. Sequences used in the steps outlined in Examples 1-5 are shown in Table 2. It should be noted that the start codon (ATG) has been underlined in each sequence of Table 2.

TABLE 2

G-CSF Sequences

SEQ ID NO	Description
1	cDNAsequence: ATGGCTGGACCTGCCACCCAGAGCCCCATGAAGCTGATGGCCCTGCAGCTGCT GCTGTGGCACAGTGCACTCTGGACAGTGCAGGAAGCCACCCCCCTGGGCCCTG CCAGCTCCCTGCCCCAGAGCTTCCTGCTCAAGTGCTTAGAGCAAGTGAGGAAG ATCCAGGGCGATGGCGCAGCGCTCCAGGAGAAGCTGGTGAGTGAGTGTGCCAC CTACAAGCTGTGCCACCCCGAGGAGCTGGTGCTGCTCGGACACTCTCTGGGCA TCCCCTGGGCTCCCCTGAGCAGCTGCCCCAGCCAGGCCCTGCAGCTGGCAGGC TGCTTGAGCCAACTCCATAGCGGCCTTTTCCTCTACCAGGGGCTCCTGCAGGCC CTGGAAGGGATCTCCCCCGAGTTGGGTCCCACCTTGGACACACTGCAGCTGGA CGTCGCCGACTTTGCCACCACCATCTGGCAGCAGATGGAAGAACTGGGAATGG CCCCTGCCCTGCAGCCCACCCAGGGTGCCATGCCGGCCTTCGCCTCTGCTTTCC AGCGCCGGGCAGGAGGGGTCCTGGTTGCCTCCCATCTGCAGAGCTTCCTGGAG GTGTCGTACCGCGTTCTACGCCACCTTGCCCAGCCCTGA
2	cDNA having T7 polymerase site and Xba restriction site: TTGGACCCTCGTACAGAAGCTAATACGACTCACTATA GGGAAATAAGAGAGAAAAGAAGAGTAAGAAGAAATATAAGAGCCACC ATGGCTGGACCTGCCACCCAGAGCCCCATGAAGCTGATGGCCCTGCAGCTGCT GCTGTGGCACAGTGCACTCTGGACAGTGCAGGAAGCCACCCCCCTGGGCCCTG CCAGCTCCCTGCCCCAGAGCTTCCTGCTCAAGTGCTTAGAGCAAGTGAGGAAG ATCCAGGGCGATGGCGCAGCGCTCCAGGAGAAGCTGGTGAGTGAGTGTGCCAC CTACAAGCTGTGCCACCCCGAGGAGCTGGTGCTGCTCGGACACTCTCTGGGCA TCCCCTGGGCTCCCCTGAGCAGCTGCCCCAGCCAGGCCCTGCAGCTGGCAGGC TGCTTGAGCCAACTCCATAGCGGCCTTTTCCTCTACCAGGGGCTCCTGCAGGCC CTGGAAGGGATCTCCCCCGAGTTGGGTCCCACCTTGGACACACTGCAGCTGGA CGTCGCCGACTTTGCCACCACCATCTGGCAGCAGATGGAAGAACTGGGAATGG CCCCTGCCCTGCAGCCCACCCAGGGTGCCATGCCGGCCTTCGCCTCTGCTTTCC AGCGCCGGGCAGGAGGGGTCCTGGTTGCCTCCCATCTGCAGAGCTTCCTGGAG GTGTCGTACCGCGTTCTACGCCACCTTGCCCAGCCCTGAAGCGCTGCCTTCTGC GGGGCTTGCCTTCTGGCCATGCCCTTCTTCTCTCCCTTGCACCTGTACCTCTTGG TCTTTGAATAAAGCCTGAGTAGGAAGGCGGCCGCTCGAGCATGCATCTAGA
3	Optimized sequence; containing T7 polymerase site and Xba restriction site TTGGACCCTCGTACAGAAGCTAATACGACTCACTATAGGGAAATAAGAGAGAA AAGAAGAGTAAGAAGAAATATAAGAGCCACC ATGGCCCTGCAGTTGCTGCTTTGGCACTCGGCCCTCTGGACAGTCCAAGAAGCG ACTCCTCTCGGACCTGCCTCATCGTTGCCGCAGTCATTCCTTTTGAAGTGTCTGG AGCAGGTGCGAAAGATTCAGGGCGATGGAGCCGCACTCCAAGAGAAGCTCTG CGCGACATACAAACTTTGCCATCCCGAGGAGCTCGTACTGCTCGGGCACAGCT TGGGGATTCCCTGGGCTCCTCTCTCGTCCTGTCCGTCGCAGGCTTTGCAGTTGG CAGGGTGCCTTTCCCAGCTCCACTCCGGTTTGTTCTTGTATCAGGGACTGCTGC AAGCCCTTGAGGGAATCTCGCCAGAATTGGGCCCGACGCTGGACACGTTGCAG CTCGACGTGGCGGATTTCGCAACAACCATCTGGCAGCAGATGGAGGAACTGGG GATGGCACCCGCGCTGCAGCCCACGCAGGGGGCAATGCCGGCCTTTGCGTCCG CGTTTCAGCGCAGGGCGGGTGGAGTCCTCGTAGCGAGCCACCTTCAATCATTTT TGGAAGTCTCGTACCGGGTGCTGAGACATCTTGCGCAGCCGTGAGCCTTCTGCG GGGCTTGCCTTCTGGCCATGCCCTTCTTCTCTCCCTTGCACCTGTACCTCTTGGT CTTTGAATAAAGCCTGAGTAGGAAGGCGGCCGCTCGAGCATGCA
4	mRNA sequence (transcribed) CUCACUAUAGGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUAAGAG CCACCA AUGGCCCUGCAGUUGCUGCUUUGGCACUCGGCCCUCUGGACAGUCCAAGAAG CGACUCCUCUCGGACCUGCCUCAUCGUUGCCGCAGUCAUUCCUUUUGAAGUG UCUGGAGCAGGUGCGAAAGAUUCAGGGCGAUGGAGCCGCACUCCAAGAGAA GCUCUGCGCGACAUACAAACUUUGCCAUCCCGAGGAGCUCGUACUGCUCGGG CACAGCUUGGGGAUUCCCUGGGCUCCUCUCUCGUCCUGUCCGUCGCAGGCUU UGCAGUUGGCAGGGUGCCUUUCCCAGCUCCACUCCGGUUUGUUCUUGUAUCA

TABLE 2-continued

G-CSF Sequences

SEQ ID NO	Description
	GGGACUGCUGCAAGCCCUUGAGGGAAUCUCGCCAGAAUUGGGCCCGACGCUG
	GACACGUUGCAGCUCGACGUGGCGGAUUUCGCAACAACCAUCUGGCAGCAGA
	UGGAGGAACUGGGGAUGGCACCCGCGCUGCAGCCCACGCAGGGGGCAAUGCC
	GGCCUUUGCGUCCGCGUUUCAGCGCAGGGCGGGUGGAGUCCUCGUAGCGAGC
	CACCUUCAAUCAUUUUUGGAAGUCUCGUACCGGGUGCUGAGACAUCUUGCG
	CAGCCGUGAGCCUUCUGCGGGGCUUGCCUUCUGGCCAUGCCCUUCUUCUCUC
	CCUUGCACCUGUACCUCUUGGUCUUUGAAUAAAGCCUGAGUAGGAAGGCGG
	CCGCUCGAGCAUGCAU

Example 2: PCR for cDNA Production

PCR procedures for the preparation of cDNA are performed using 2×KAPA HIFI™ HotStart ReadyMix by Kapa Biosystems (Woburn, Mass.). This system includes 2×KAPA ReadyMix12.5 μl; Forward Primer (10 uM) 0.75 μl; Reverse Primer (10 uM) 0.75 μl; Template cDNA 100 ng; and dH_2O diluted to 25.0 μl. The reaction conditions are at 95° C. for 5 min. and 25 cycles of 98° C. for 20 sec, then 58° C. for 15 sec, then 72° C. for 45 sec, then 72° C. for 5 min. then 4° C. to termination.

The reverse primer of the instant invention incorporates a poly-T_{120} for a poly-A_{120} in the mRNA. Other reverse primers with longer or shorter poly(T) tracts can be used to adjust the length of the poly(A) tail in the mRNA.

The reaction is cleaned up using Invitrogen's PURELINK™ PCR Micro Kit (Carlsbad, Calif.) per manufacturer's instructions (up to 5 μg). Larger reactions will require a cleanup using a product with a larger capacity. Following the cleanup, the cDNA is quantified using the NanoDrop and analyzed by agarose gel electrophoresis to confirm the cDNA is the expected size. The cDNA is then submitted for sequencing analysis before proceeding to the in vitro transcription reaction.

Example 3. In Vitro Transcription (IVT)

The in vitro transcription reaction generates mRNA containing modified nucleotides or modified RNA. The input nucleotide triphosphate (NTP) mix is made in-house using natural and un-natural NTPs.

A typical in vitro transcription reaction includes the following:

1.	Template cDNA	1.0 μg
2.	10x transcription buffer (400 mM Tris-HCl pH 8.0, 190 mM $MgCl_2$, 50 mM DTT, 10 mM Spermidine)	2.0 μl
3.	Custom NTPs (25 mM each)	7.2 μl
4.	RNase Inhibitor	20 U
5.	T7 RNA polymerase	3000 U
6.	dH_20	Up to 20.0 μl. and
7.	Incubation at 37° C. for 3 hr-5 hrs.	

The crude IVT mix may be stored at 4° C. overnight for cleanup the next day. 1 U of RNase-free DNase is then used to digest the original template. After 15 minutes of incubation at 37° C., the mRNA is purified using Ambion's MEGACLEAR™ Kit (Austin, Tex.) following the manufacturer's instructions. This kit can purify up to 500 μg of RNA. Following the cleanup, the RNA is quantified using the NanoDrop and analyzed by agarose gel electrophoresis to confirm the RNA is the proper size and that no degradation of the RNA has occurred.

Example 4. Enzymatic Capping of mRNA

Capping of the mRNA is performed as follows where the mixture includes: IVT RNA 60 μg-180 μg and dH_2O up to 72 μl. The mixture is incubated at 65° C. for 5 minutes to denature RNA, and then is transferred immediately to ice.

The protocol then involves the mixing of 10× Capping Buffer (0.5 M Tris-HCl (pH 8.0), 60 mM KCl, 12.5 mM $MgCl_2$) (10.0 μl); 20 mM GTP (5.0 μl); 20 mM S-Adenosyl Methionine (2.5 μl); RNase Inhibitor (100 U); 2'-O-Methyltransferase (400 U); Vaccinia capping enzyme (Guanylyl transferase) (40 U); dH_2O (Up to 28 μl); and incubation at 37° C. for 30 minutes for 60 μg RNA or up to 2 hours for 180 μg of RNA.

The mRNA is then purified using Ambion's MEGACLEAR™ Kit (Austin, Tex.) following the manufacturer's instructions. Following the cleanup, the RNA is quantified using the NANODROP™ (ThermoFisher, Waltham, Mass.) and analyzed by agarose gel electrophoresis to confirm the RNA is the proper size and that no degradation of the RNA has occurred. The RNA product may also be sequenced by running a reverse-transcription-PCR to generate the cDNA for sequencing.

Example 5. PolyA Tailing Reaction

Without a poly-T in the cDNA, a poly-A tailing reaction must be performed before cleaning the final product. This is done by mixing Capped IVT RNA (100 μl); RNase Inhibitor (20 U); 10× Tailing Buffer (0.5 M Tris-HCl (pH 8.0), 2.5 M NaCl, 100 mM $MgCl_2$)(12.0 μl); 20 mM ATP (6.0 μl); Poly-A Polymerase (20 U); dH_2O up to 123.5 μl and incubation at 37° C. for 30 min. If the poly-A tail is already in the transcript, then the tailing reaction may be skipped and proceed directly to cleanup with Ambion's MEGACLEAR™ kit (Austin, Tex.) (up to 500 μg). Poly-A Polymerase is preferably a recombinant enzyme expressed in yeast.

For studies performed and described herein, the poly-A tail is encoded in the IVT template to comprise 160 nucleotides in length. However, it should be understood that the processivity or integrity of the Poly-A tailing reaction may not always result in exactly 160 nucleotides. Hence Poly-A tails of approximately 160 nucleotides, e.g, about 150-165,

155, 156, 157, 158, 159, 160, 161, 162, 163, 164 or 165 are within the scope of the invention.

Example 6. Formulation of Modified mRNA Using Lipidoids

5'-capping of modified RNA may be completed concomitantly during the in vitro-transcription reaction using the following chemical RNA cap analogs to generate the 5'-guanosine cap structure according to manufacturer protocols: 3'-O-Me-m7G(5')ppp(5') G [the ARCA cap]; G(5')ppp(5')A; G(5')ppp(5')G; m7G(5')ppp(5')A; m7G(5')ppp(5')G (New England BioLabs, Ipswich, Mass.). 5'-capping of modified RNA may be completed post-transcriptionally using a Vaccinia Virus Capping Enzyme to generate the "Cap 0" structure: m7G(5')ppp(5')G (New England BioLabs, Ipswich, Mass.). Cap 1 structure may be generated using both Vaccinia Virus Capping Enzyme and a 2'-O methyl-transferase to generate: m7G(5')ppp(5')G-2'-O-methyl. Cap 2 structure may be generated from the Cap 1 structure followed by the 2'-O-methylation of the 5'-antepenultimate nucleotide using a 2'-O methyl-transferase. Cap 3 structure may be generated from the Cap 2 structure followed by the 2'-O-methylation of the 5'-preantepenultimate nucleotide using a 2'-O methyl-transferase. Enzymes are preferably derived from a recombinant source.

When transfected into mammalian cells, the modified mRNAs have a stability of between 12-18 hours or more than 18 hours, e.g., 24, 36, 48, 60, 72 or greater than 72 hours.

Example 7. Capping

A. Protein Expression Assay

Synthetic mRNAs encoding human G-CSF (cDNA shown in SEQ ID NO: 1) containing the ARCA (3' O-Me-m7G(5')ppp(5')G) cap analog or the Cap1 structure can be transfected into human primary keratinocytes at equal concentrations. 6, 12, 24 and 36 hours post-transfection the amount of G-CSF secreted into the culture medium can be assayed by ELISA. Synthetic mRNAs that secrete higher levels of G-CSF into the medium would correspond to a synthetic mRNA with a higher translationally-competent Cap structure.

B. Purity Analysis Synthesis

mRNAs encoding human G-CSF (cDNA shown in SEQ ID NO: 1) containing the ARCA cap analog or the Cap1 structure crude synthesis products can be compared for purity using denaturing Agarose-Urea gel electrophoresis or HPLC analysis. Synthetic mRNAs with a single, consolidated band by electrophoresis correspond to the higher purity product compared to a synthetic mRNA with multiple bands or streaking bands. Synthetic mRNAs with a single HPLC peak would also correspond to a higher purity product. The capping reaction with a higher efficiency would provide a more pure mRNA population.

C. Cytokine Analysis

Synthetic mRNAs encoding human G-CSF (cDNA shown in SEQ ID NO: 1) containing the ARCA cap analog or the Cap1 structure can be transfected into human primary keratinocytes at multiple concentrations. 6, 12, 24 and 36 hours post-transfection the amount of pro-inflammatory cytokines such as TNF-alpha and IFN-beta secreted into the culture medium can be assayed by ELISA. Synthetic mRNAs that secrete higher levels of pro-inflammatory cytokines into the medium would correspond to a synthetic mRNA containing an immune-activating cap structure.

D. Capping Reaction Efficiency

Synthetic mRNAs encoding human G-CSF (cDNA shown in SEQ ID NO: 1) containing the ARCA cap analog or the Cap1 structure can be analyzed for capping reaction efficiency by LC-MS after capped mRNA nuclease treatment. Nuclease treatment of capped mRNAs would yield a mixture of free nucleotides and the capped 5'-5-triphosphate cap structure detectable by LC-MS. The amount of capped product on the LC-MS spectra can be expressed as a percent of total mRNA from the reaction and would correspond to capping reaction efficiency. The cap structure with a higher capping reaction efficiency would have a higher amount of capped product by LC-MS.

Example 8. Formulation of Modified mRNA Using Lipidoids

Modified mRNAs (mmRNA) are formulated for in vitro experiments by mixing the mmRNA with the lipidoid at a set ratio prior to addition to cells. In vivo formulation may require the addition of extra ingredients to facilitate circulation throughout the body. To test the ability of these lipidoids to form particles suitable for in vivo work, a standard formulation process used for siRNA-lipidoid formulations was used as a starting point. Initial mmRNA-lipidoid formulations may consist of particles composed of 42% lipidoid, 48% cholesterol and 10% PEG, with further optimization of ratios possible. After formation of the particle, mmRNA is added and allowed to integrate with the complex. The encapsulation efficiency is determined using a standard dye exclusion assays.

Materials and Methods for Examples 9-13

A. Lipid Synthesis

Six lipids, DLin-DMA, DLin-K-DMA, DLin-KC2-DMA, 98N12-5, C12-200 and DLin-MC3-DMA, were synthesized by methods outlined in the art in order to be formulated with modified RNA. DLin-DMA and precursors were synthesized as described in Heyes et. al, J. Control Release, 2005, 107, 276-287. DLin-K-DMA and DLin-KC2-DMA and precursors were synthesized as described in Semple et. al, Nature Biotechnology, 2010, 28, 172-176. 98N12-5 and precursor were synthesized as described in Akinc et. al, *Nature Biotechnology,* 2008, 26, 561-569.

C12-200 and precursors were synthesized according to the method outlined in Love et. al, PNAS, 2010, 107, 1864-1869. 2-epoxydodecane (5.10 g, 27.7 mmol, 8.2 eq) was added to a vial containing Amine 200 (0.723 g, 3.36 mmol, 1 eq) and a stirring bar. The vial was sealed and warmed to 80° C. The reaction was stirred for 4 days at 80° C. Then the mixture was purified by silica gel chromatography using a gradient from pure dichloromethane (DCM) to DCM:MeOH 98:2. The target compound was further purified by RP-HPLC to afford the desired compound.

DLin-MC3-DMA and precursors were synthesized according to procedures described in WO 2010054401 herein incorporated by reference in its entirety. A mixture of dilinoleyl methanol (1.5 g, 2.8 mmol, 1 eq), N,N-dimethylaminobutyric acid (1.5 g, 2.8 mmol, 1 eq), DIPEA (0.73 mL, 4.2 mmol, 1.5 eq) and TBTU (1.35 g, 4.2 mmol, 1.5 eq) in 10 mL of DMF was stirred for 10 h at room temperature. Then the reaction mixture was diluted in ether and washed with water. The organic layer was dried over anhydrous sodium sulfate, filtrated and concentrated under reduced pressure. The crude product was purified by silica gel chromatography using a gradient DCM to DCM:MeOH 98:2. Subsequently the target compound was subjected to an

additional RP-HPLC purification which was done using a YMC—Pack C4 column to afford the target compound.

B. Formulation of Modified RNA Nanoparticles

Solutions of synthesized lipid, 1,2-distearoyl-3-phosphatidylcholine (DSPC) (Avanti Polar Lipids, Alabaster, Ala.), cholesterol (Sigma-Aldrich, Taufkirchen, Germany), and α-[3'-(1,2-dimyristoyl-3-propanoxy)-carboxamide-propyl]-ω-methoxy-polyoxyethylene (PEG-c-DOMG) (NOF, Bouwelven, Belgium) were prepared at concentrations of 50 mM in ethanol and stored at −20° C. The lipids were combined to yield molar ratio of 50:10:38.5:1.5 (Lipid: DSPC: Cholesterol: PEG-c-DOMG) and diluted with ethanol to a final lipid concentration of 25 mM. Solutions of modified mRNA at a concentration of 1-2 mg/mL in water were diluted in 50 mM sodium citrate buffer at a pH of 3 to form a stock modified mRNA solution. Formulations of the lipid and modified mRNA were prepared by combining the synthesized lipid solution with the modified mRNA solution at total lipid to modified mRNA weight ratio of 10:1, 15:1, 20:1 and 30:1. The lipid ethanolic solution was rapidly injected into aqueous modified mRNA solution to afford a suspension containing 33% ethanol. The solutions were injected either manually (MI) or by the aid of a syringe pump (SP) (Harvard Pump 33 Dual Syringe Pump Harvard Apparatus Holliston, Mass.).

To remove the ethanol and to achieve the buffer exchange, the formulations were dialyzed twice against phosphate buffered saline (PBS), pH 7.4 at volumes 200-times of the primary product using a Slide-A-Lyzer cassettes (Thermo Fisher Scientific Inc. Rockford, Ill.) with a molecular weight cutoff (MWCO) of 10 kD. The first dialysis was carried at room temperature for 3 hours and then the formulations were dialyzed overnight at 4° C. The resulting nanoparticle suspension was filtered through 0.2 μm sterile filter (Sarstedt, Niimbrecht, Germany) into glass vials and sealed with a crimp closure.

C. Characterization of Formulations

A Zetasizer Nano ZS (Malvern Instruments Ltd, Malvern, Worcestershire, UK) was used to determine the particle size, the polydispersity index (PDI) and the zeta potential of the modified mRNA nanoparticles in 1×PBS in determining particle size and 15 mM PBS in determining zeta potential.

Ultraviolet-visible spectroscopy was used to determine the concentration of modified mRNA nanoparticle formulation. 100 μL of the diluted formulation in 1×PBS was added to 900 μL of a 4:1 (v/v) mixture of methanol and chloroform. After mixing, the absorbance spectrum of the solution was recorded between 230 nm and 330 nm on a DU 800 spectrophotometer (Beckman Coulter, Beckman Coulter, Inc., Brea, Calif.). The modified RNA concentration in the nanoparticle formulation was calculated based on the extinction coefficient of the modified RNA used in the formulation and on the difference between the absorbance at a wavelength of 260 nm and the baseline value at a wavelength of 330 nm.

QUANT-IT™ RIBOGREEN® RNA assay (Invitrogen Corporation Carlsbad, Calif.) was used to evaluate the encapsulation of modified RNA by the nanoparticle. The samples were diluted to a concentration of approximately 5 μg/mL in TE buffer (10 mM Tris-HCl, 1 mM EDTA, pH 7.5). 50 μL of the diluted samples were transferred to a polystyrene 96 well plate, then either 50 μL of TE buffer or 50 μL of a 2% Triton X-100 solution was added. The plate was incubated at a temperature of 37° C. for 15 minutes. The RIBOGREEN® reagent was diluted 1:100 in TE buffer, 100 μL of this solution was added to each well. The fluorescence intensity was measured using a fluorescence plate reader (Wallac Victor 1420 Multilablel Counter; Perkin Elmer, Waltham, Mass.) at an excitation wavelength of ~480 nm and an emission wavelength of ~520 nm. The fluorescence values of the reagent blank were subtracted from that of each of the samples and the percentage of free modified RNA was determined by dividing the fluorescence intensity of the intact sample (without addition of Triton X-100) by the fluorescence value of the disrupted sample (caused by the addition of Triton X-100).

D. In Vitro Incubation

Human embryonic kidney epithelial (HEK293) and hepatocellular carcinoma epithelial (HepG2) cells (LGC standards GmbH, Wesel, Germany) were seeded on 96-well plates (Greiner Bio-one GmbH, Frickenhausen, Germany) and plates for HEK293 cells were precoated with collagen type1. HEK293 were seeded at a density of 30,000 and HepG2 were seeded at a density of 35,000 cells per well in 100 μl cell culture medium. For HEK293 the cell culture medium was DMEM, 10% FCS, adding 2 mM L-Glutamine, 1 mM Sodiumpyruvate and 1× non-essential amino acids (Biochrom AG, Berlin, Germany) and 1.2 mg/ml Sodiumbicarbonate (Sigma-Aldrich, Munich, Germany) and for HepG2 the culture medium was MEM (Gibco Life Technologies, Darmstadt, Germany), 10% FCS adding 2 mM L-Glutamine, 1 mM Sodiumpyruvate and 1× non-essential amino acids (Biochrom AG, Berlin, Germany. Formulations containing mCherry mRNA (mRNA sequence shown in SEQ ID NO: 5; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1) were added in quadruplicates directly after seeding the cells and incubated. The mCherry cDNA with the T7 promoter, 5'untranslated region (UTR) and 3' UTR used in in vitro transcription (IVT) is given in SEQ ID NO: 6.

Cells were harvested by transferring the culture media supernatants to a 96-well Pro-Bind U-bottom plate (Beckton Dickinson GmbH, Heidelberg, Germany). Cells were trypsinized with ½ volume Trypsin/EDTA (Biochrom AG, Berlin, Germany), pooled with respective supernatants and fixed by adding one volume PBS/2% FCS (both Biochrom AG, Berlin, Germany)/0.5% formaldehyde (Merck, Darmstadt, Germany). Samples then were submitted to a flow cytometer measurement with a 532 nm excitation laser and the 610/20 filter for PE-Texas Red in a LSRII cytometer (Beckton Dickinson GmbH, Heidelberg, Germany). The mean fluorescence intensity (MFI) of all events and the standard deviation of four independent wells are presented in for samples analyzed.

Example 9. Purification on Nanoparticle Formulations

Nanoparticle formulations of DLin-KC2-DMA and 98N12-5 in HEK293 and HepG2 were tested to determine if the mean fluorescent intensity (MFI) was dependent on the lipid to modified RNA ratio and/or purification. Three formulations of DLin-KC2-DMA and two formulations of 98N12-5 were produced using a syringe pump to the specifications described in Table 3. Purified samples were purified by SEPHADEX™ G-25 DNA grade (GE Healthcare, Sweden). Each formulation before and after purification (aP) were tested at concentration of 250 ng modified RNA per well in a 24 well plate. The percentage of cells that are positive for the marker for FL4 channel (% FL4-positive) when analyzed by the flow cytometer for each formulation and the background sample are shown in FIGS. **3**A and **3**B, and the MFI of the marker for the FL4 channel for each formulation and the background sample are shown in FIGS.

4A and 4B. The formulations which had been purified had a slightly higher MFI than those formulations tested before purification.

TABLE 3

Formulations

Formulation #	Lipid	Lipid/RNA wt/wt	Mean size (nm)
NPA-001-1	DLin-KC2-DMA	10	155 nm PDI: 0.08
NPA-001-1 aP	DLin-KC2-DMA	10	141 nm PDI: 0.14
NPA-002-1	DLin-KC2-DMA	15	140 nm PDI: 0.11
NPA-002-1 aP	DLin-KC2-DMA	15	125 nm PDI: 0.12
NPA-003-1	DLin-KC2-DMA	20	114 nm PDI: 0.08
NPA-003-1 aP	DLin-KC2-DMA	20	104 nm PDI: 0.06
NPA-005-1	98N12-5	15	127 nm PDI: 0.12
NPA-005-1 aP	98N12-5	15	134 nm PDI: 0.17
NPA-006-1	98N12	20	126 nm PDI: 0.08
NPA-006-1 aP	98N12	20	118 nm PDI: 0.13

Example 10. Concentration Response Curve

Nanoparticle formulations of 98N12-5 (NPA-005) and DLin-KC2-DMA (NPA-003) were tested at varying concentrations to determine the MFI of FL4 or mCherry (mRNA sequence shown in SEQ ID NO: 5; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1) over a range of doses. The formulations tested are outlined in Table 4. To determine the optimal concentration of nanoparticle formulations of 98N12-5, varying concentrations of formulated modified RNA (100 ng, 10 ng, 1.0 ng, 0.1 ng and 0.01 ng per well) were tested in a 24-well plate of HEK293, and the results of the FL4 MFI of each dose are shown in FIG. 5A. Likewise, to determine the optimal concentration of nanoparticle formulations of DLin-KC2-DMA, varying concentrations of formulated modified RNA (250 ng 100 ng, 10 ng, 1.0 ng, 0.1 ng and 0.01 ng per well) were tested in a 24-well plate of HEK293, and the results of the FL4 MFI of each dose are shown in FIG. 5B. Nanoparticle formulations of DLin-KC2-DMA were also tested at varying concentrations of formulated modified RNA (250 ng, 100 ng and 30 ng per well) in a 24 well plate of HEK293, and the results of the FL4 MFI of each dose are shown in FIG. 5C. A dose of 1 ng/well for 98N12-5 and a dose of 10 ng/well for DLin-K2-DMA were found to resemble the FL4 MFI of the background.

To determine how close the concentrations resembled the background, we utilized a flow cytometer with optimized filter sets for detection of mCherry expression, and were able to obtain results with increased sensitivity relative to background levels. Doses of 25 ng/well, 0.25 ng/well, 0.025 ng/well and 0.0025 ng/well were analyzed for 98N12-5 (NPA-005) and DLin-K2-DMA (NPA-003) to determine the MFI of mCherry. As shown in Table 5, the concentration of 0.025 ng/well and lesser concentrations are similar to the background MFI level of mCherry which is about 386.125.

TABLE 4

Formulations

	Formulation #	
	NPA-003	NPA-005
Lipid	DLin-KC2-DMA	98N12-5
Lipid/RNA wt/wt	20	15
Mean size	114 nm PDI: 0.08	106 nm PDI: 0.12

TABLE 5

Concentration and MFI

	MFI mCherry	
Formulation	NPA-003	NPA-005
25 ng/well	11963.25	12256.75
0.25 ng/well	1349.75	2572.75
0.025 ng/well	459.50	534.75
0.0025 ng/well	310.75	471.75

Example 11. Manual Injection and Syringe Pump Formulations

Two formulations of DLin-KC2-DMA and 98N12-5 were prepared by manual injection (MI) and syringe pump injection (SP) and analyzed along with a background sample to compare the MFI of mCherry (mRNA shown in SEQ ID NO: 5; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1) of the different formulations. Table 5 shows that the syringe pump formulations had a higher MFI as compared to the manual injection formulations of the same lipid and lipid/RNA ratio.

TABLE 5

Formulations and MFI

Formulation #	Lipid	Lipid/RNA wt/wt	Mean size (nm)	Method of formulation	MFI
Untreated Control	N/A	N/A	N/A	N/A	674.67
NPA-002	DLin-KC2-DMA	15	140 nm PDI: 0.11	MI	10318.25
NPA-002-2	DLin-KC2-DMA	15	105 nm PDI: 0.04	SP	37054.75
NPA-003	DLin-KC2-DMA	20	114 nm PDI: 0.08	MI	22037.5
NPA-003-2	DLin-KC2-DMA	20	95 nm PDI: 0.02	SP	37868.75
NPA-005	98N12-5	15	127 nm PDI: 0.12	MI	11504.75
NPA-005-2	98N12-5	15	106 nm PDI: 0.07	SP	9343.75
NPA-006	98N12-5	20	126 nm PDI: 0.08	MI	11182.25
NPA-006-2	98N12-5	20	93 nm PDI: 0.08	SP	5167

Example 12. mCherry Fluorescence of Formulations

Formulations of DLin-DMA, DLin-K-DMA, DLin-KC2-DMA, 98N12-5, C12-200 and DLin-MC3-DMA were incu-

bated at a concentration of 60 ng/well or 62.5 ng/well in a plate of HEK293 and 62.5 ng/well in a plate of HepG2 cells for 24 hours to determine the MFI of mCherry (mRNA shown in SEQ ID NO: 5; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1) for each formulation. The formulations tested are outlined in Table 6 below. As shown in FIG. **6**A for the 60 ng/well and FIGS. **6**B, **6**C, **6**D, and **6**E for the 62.5 ng/well, the formulation of NPA-003 and NPA-018 have the highest mCherry MFI and the formulations of NPA-008, NPA-010 and NPA-013 are most the similar to the background sample mCherry MFI value.

TABLE 6

Formulations

Formulation #	Lipid	Lipid/RNA wt/wt	Mean size (nm)
NPA-001	DLin-KC2-DMA	10	155 nm PDI: 0.08
NPA-002	DLin-KC2-DMA	15	140 nm PDI: 0.11
NPA-002-2	DLin-KC2-DMA	15	105 nm PDI: 0.04
NPA-003	DLin-KC2-DMA	20	114 nm PDI: 0.08
NPA-003-2	DLin-KC2-DMA	20	95 nm PDI: 0.02
NPA-005	98N12-5	15	127 nm PDI: 0.12
NPA-006	98N12-5	20	126 nm PDI: 0.08
NPA-007	DLin-DMA	15	148 nm PDI: 0.09
NPA-008	DLin-K-DMA	15	121 nm PDI: 0.08
NPA-009	C12-200	15	138 nm PDI: 0.15
NPA-010	DLin-MC3-DMA	15	126 nm PDI: 0.09
NPA-012	DLin-DMA	20	86 nm PDI: 0.08
NPA-013	DLin-K-DMA	20	104 nm PDI: 0.03
NPA-014	C12-200	20	101 nm PDI: 0.06
NPA-015	DLin-MC3-DMA	20	109 nm PDI: 0.07

Example 13. In Vivo Formulation Studies

Mice (n=5) are administered intravenously a single dose of a formulation containing a modified mRNA and a lipid. The modified mRNA administered to the mice is selected from G-CSF (mRNA shown in SEQ ID NO: 4; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1), erythropoietin (EPO) (mRNA shown in SEQ ID NO: 7; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1), Factor IX (mRNA shown in SEQ ID NO: 8; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1) or mCherry (mRNA sequence shown in SEQ ID NO: 5; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1). The erythropoietin cDNA with the T7 promoter, 5'untranslated region (UTR) and 3' UTR used in in vitro transcription (IVT) is given in SEQ ID NO: 9.

Each formulation also contains a lipid which is selected from one of DLin-DMA, DLin-K-DMA, DLin-KC2-DMA, 98N12-5, C12-200 or DLin-MC3-DMA. The mice are injected with 100 ug, 10 ug or 1 ug of the formulated modified mRNA and are sacrificed 8 hours after they are administered the formulation. Serum from the mice administered formulations containing human G-CSF modified mRNA are measured by specific G-CSF ELISA and serum from mice administered human Factor IX modified RNA is analyzed by specific Factor IX ELISA or chromogenic assay. The liver and spleen from the mice administered with mCherry modified mRNA are analyzed by immunohistochemistry (IHC) or fluorescence-activated cell sorting (FACS). As a control, a group of mice are not injected with any formulation and their serum and tissue are collected analyzed by ELISA, FACS and/or IHC.

Example 14. In Vitro and In Vivo Expression

A. A. In Vitro Expression in Human Cells Using Lipidoid Formulations

The ratio of mmRNA to lipidoid used to test for in vitro transfection is tested empirically at different lipidoid:mmRNA ratios. Previous work using siRNA and lipidoids have utilized 2.5:1, 5:1, 10:1, and 15:1 lipidoid:siRNA wt:wt ratios. Given the longer length of mmRNA relative to siRNA, a lower wt:wt ratio of lipidoid to mmRNA may be effective. In addition, for comparison mmRNA were also formulated using RNAIMAX™ (Invitrogen, Carlsbad, Calif.) or TRANSIT-mRNA (Mirus Bio, Madison, Wis.) cationic lipid delivery vehicles. The ability of lipidoid-formulated Luciferase (IVT cDNA sequence as shown in SEQ ID NO: 10), green fluorescent protein (GFP) (IVT cDNA sequence as shown in SEQ ID NO: 11), G-CSF (mRNA sequence shown in SEQ ID NO: 4; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1), and EPO mmRNA (mRNA sequence shown in SEQ ID NO: 7; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1) to express the desired protein product can be confirmed by luminescence for luciferase expression, flow cytometry for GFP expression, and by ELISA for G-CSF and Erythropoietin (EPO) secretion.

B. In Vivo Expression Following Intravenous Injection

Systemic intravenous administration of the formulations are created using various different lipidoids including, but not limited to, 98N12-5, C12-200, and MD1.

Lipidoid formulations containing mmRNA are injected intravenously into animals. The expression of the modified mRNA (mmRNA)-encoded proteins are assessed in blood and/or other organs samples such as, but not limited to, the liver and spleen collected from the animal. Conducting single dose intravenous studies will also allow an assessment of the magnitude, dose responsiveness, and longevity of expression of the desired product.

In one embodiment, lipidoid based formulations of 98N12-5, C12-200, MD1 and other lipidoids, are used to deliver luciferase, green fluorescent protein (GFP), mCherry fluorescent protein, secreted alkaline phosphatase (sAP), human G-CSF, human Factor IX, or human Erythropoietin (EPO) mmRNA into the animal. After formulating mmRNA with a lipid, as described previously, animals are divided into groups to receive either a saline formulation, or a lipidoid-formulation which contains one of a different mmRNA selected from luciferase, GFP, mCherry, sAP, human G-CSF, human Factor IX, and human EPO. Prior to injection into the animal, mmRNA-containing lipidoid formulations are diluted in PBS. Animals are then administered a single dose of formulated mmRNA ranging from a dose of 10 mg/kg to doses as low as 1 ng/kg, with a preferred range to be 10 mg/kg to 100 ng/kg, where the dose of mmRNA depends on the animal body weight such as a 20 gram mouse receiving a maximum formulation of 0.2 ml (dosing is based no mmRNA per kg body weight). After the administration of the mmRNA-lipidoid formulation, serum, tissues, and/or tissue lysates are obtained and the level of the mmRNA-

encoded product is determined at a single and/or a range of time intervals. The ability of lipidoid-formulated Luciferase, GFP, mCherry, sAP, G-CSF, Factor IX, and EPO mmRNA to express the desired protein product is confirmed by luminescence for the expression of Luciferase, flow cytometry for the expression of GFP and mCherry expression, by enzymatic activity for sAP, or by ELISA for the section of G-CSF, Factor IX and/or EPO.

Further studies for a multi-dose regimen are also performed to determine the maximal expression of mmRNA, to evaluate the saturability of the mmRNA-driven expression (by giving a control and active mmRNA formulation in parallel or in sequence), and to determine the feasibility of repeat drug administration (by giving mmRNA in doses separated by weeks or months and then determining whether expression level is affected by factors such as immunogenicity). An assessment of the physiological function of proteins such as G-CSF and EPO are also determined through analyzing samples from the animal tested and detecting increases in granulocyte and red blood cell counts, respectively. Activity of an expressed protein product such as Factor IX, in animals can also be assessed through analysis of Factor IX enzymatic activity (such as an activated partial thromboplastin time assay) and effect of clotting times.

C. In Vitro Expression Following Intramuscular and/or Subcutaneous Injection

The use of lipidoid formulations to deliver oligonucleotides, including mRNA, via an intramuscular route or a subcutaneous route of injection needs to be evaluated as it has not been previously reported. Intramuscular and/or subcutaneous injection of mmRNA are evaluated to determine if mmRNA-containing lipidoid formulations are capable to produce both localized and systemic expression of a desired portions.

Lipidoid formulations of 98N12-5, C12-200, and MD1 containing mmRNA selected from luciferase, green fluorescent protein (GFP), mCherry fluorescent protein, secreted alkaline phosphatase (sAP), human G-CSF, human factor IX, or human Erythropoietin (EPO) mmRNA are injected intramuscularly and/or subcutaneously into animals. The expression of mmRNA-encoded proteins are assessed both within the muscle or subcutaneous tissue and systemically in blood and other organs such as the liver and spleen. Single dose studies allow an assessment of the magnitude, dose responsiveness, and longevity of expression of the desired product.

Animals are divided into groups to receive either a saline formulation or a formulation containing modified mRNA. Prior to injection mmRNA-containing lipidoid formulations are diluted in PBS. Animals are administered a single intramuscular dose of formulated mmRNA ranging from 50 mg/kg to doses as low as 1 ng/kg with a preferred range to be 10 mg/kg to 100 ng/kg. A maximum dose for intramuscular administration, for a mouse, is roughly 1 mg mmRNA or as low as 0.02 ng mmRNA for an intramuscular injection into the hind limb of the mouse. For subcutaneous administration, the animals are administered a single subcutaneous dose of formulated mmRNA ranging from 400 mg/kg to doses as low as 1 ng/kg with a preferred range to be 80 mg/kg to 100 ng/kg. A maximum dose for subcutaneous administration, for a mouse, is roughly 8 mg mmRNA or as low as 0.02 ng mmRNA.

For a 20 gram mouse the volume of a single intramuscular injection is maximally 0.025 ml and a single subcutaneous injection is maximally 0.2 ml. The optimal dose of mmRNA administered is calculated from the body weight of the animal. At various points in time points following the administration of the mmRNA-lipidoid, serum, tissues, and tissue lysates is obtained and the level of the mmRNA-encoded product is determined. The ability of lipidoid-formulated luciferase, green fluorescent protein (GFP), mCherry fluorescent protein, secreted alkaline phosphatase (sAP), human G-CSF, human factor IX, or human Erythropoietin (EPO) mmRNA to express the desired protein product is confirmed by luminescence for luciferase expression, flow cytometry for GFP and mCherry expression, by enzymatic activity for sAP, and by ELISA for G-CSF, Factor IX and Erythropoietin (EPO) secretion.

Additional studies for a multi-dose regimen are also performed to determine the maximal expression using mmRNA, to evaluate the saturability of the mmRNA-driven expression (achieved by giving a control and active mmRNA formulation in parallel or in sequence), and to determine the feasibility of repeat drug administration (by giving mmRNA in doses separated by weeks or months and then determining whether expression level is affected by factors such as immunogenicity). Studies utilizing multiple subcutaneous or intramuscular injection sites at one time point, are also utilized to further increase mmRNA drug exposure and improve protein production. An assessment of the physiological function of proteins, such as GFP, mCherry, sAP, human G-CSF, human factor IX, and human EPO, are determined through analyzing samples from the tested animals and detecting a change in granulocyte and/or red blood cell counts. Activity of an expressed protein product such as Factor IX, in animals can also be assessed through analysis of Factor IX enzymatic activity (such as an activated partial thromboplastin time assay) and effect of clotting times.

Example 15. Split Dose Studies

Studies utilizing multiple subcutaneous or intramuscular injection sites at one time point were designed and performed to investigate ways to increase mmRNA drug exposure and improve protein production. In addition to detection of the expressed protein product, an assessment of the physiological function of proteins was also determined through analyzing samples from the animal tested.

Surprisingly, it has been determined that split dosing of mmRNA produces greater protein production and phenotypic responses than those produced by single unit dosing or multi-dosing schemes.

The design of a single unit dose, multi-dose and split dose experiment involved using human erythropoietin (EPO) mmRNA (mRNA sequence shown in SEQ ID NO: 7; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1) administered in buffer alone. The dosing vehicle (F. buffer) consisted of 150 mM NaCl, 2 mM $CaCl_2$, 2 mM Na^+-phosphate (1.4 mM monobasic sodium phosphate; 0.6 mM dibasic sodium phosphate), and 0.5 mM EDTA, pH 6.5. The pH was adjusted using sodium hydroxide and the final solution was filter sterilized. The mmRNA was modified with 5meC at each cytosine and pseudouridine replacement at each uridine site.

Animals (n=5) were injected IM (intramuscular) for the single unit dose of 100 ug. For multi-dosing, two schedules were used, 3 doses of 100 ug and 6 doses of 100 ug. For the split dosing scheme, two schedules were used, 3 doses at 33.3 ug and 6 doses of 16.5 ug mmRNA. Control dosing involved use of buffer only at 6 doses. Control mmRNA involved the use of luciferase mmRNA (IVT cDNA sequence shown in SEQ ID NO: 10) dosed 6 times at 100 ug. Blood and muscle tissue were evaluated 13 hrs post injection.

Human EPO protein was measured in mouse serum 13 h post I.M. single, multi- or split dosing of the EPO mmRNA in buffer. Seven groups of mice (n=5 mice per group) were treated and evaluated. The results are shown in Table 7.

TABLE 7

Split dose study

Group	Treatment	Dose of mmRNA	Total Dose	Avg. pmol/mL human EPO	Polypeptide per unit drug (pmol/ug)	Dose Splitting Factor
1	Human EPO mmRNA	1 × 100 ug	100 ug	14.3	.14	1
2	Human EPO mmRNA	3 × 100 ug	300 ug	82.5	.28	2
3	Human EPO mmRNA	6 × 100 ug	600 ug	273.0	.46	3.3
4	Human EPO mmRNA	3 × 33.3 ug	100 ug	104.7	1.1	7.9
5	Human EPO mmRNA	6 × 16.5 ug	100 ug	127.9	1.3	9.3
6	Luciferase mmRNA	6 × 100 ug	600 ug	0	—	—
7	Buffer Alone	—	—	0	—	—

The splitting factor is defined as the product per unit drug divided by the single dose product per unit drug (PUD). For example for treatment group 2 the value 0.28 or product (EPO) per unit drug (mmRNA) is divided by the single dose product per unit drug of 0.14. The result is 2. Likewise, for treatment group 4, the value 1.1 or product (EPO) per unit drug (mmRNA) is divided by the single dose product per unit drug of 0.14. The result is 7.9. Consequently, the dose splitting factor (DSF) may be used as an indicator of the efficacy of a split dose regimen. For any single administration of a total daily dose, the DSF should be equal to 1. Therefore any DSF greater than this value in a split dose regimen is an indication of increased efficacy.

To determine the dose response trends, impact of injection site and impact of injection timing, studies are performed. In these studies, varied doses of 1 ug, 5 ug, 10 ug, 25 ug, 50 ug, and values in between are used to determine dose response outcomes. Split dosing for a 100 ug total dose includes three or six doses of 1.6 ug, 4.2 ug, 8.3 ug, 16.6 ug, or values and total doses equal to administration of the total dose selected.

Injection sites are chosen from the limbs or any body surface presenting enough area suitable for injection. This may also include a selection of injection depth to target the dermis (Intradermal), epidermis (Epidermal), subcutaneous tissue (SC) or muscle (IM). Injection angle will vary based on targeted delivery site with injections targeting the intradermal site to be 10-15 degree angles from the plane of the surface of the skin, between 20-45 degrees from the plane of the surface of the skin for subcutaneous injections and angles of between 60-90 degrees for injections substantially into the muscle.

Example 16: Dose Response and Injection Site Selection and Timing

To determine the dose response trends, impact of injection site and impact of injection timing, studies are performed following the protocol outlined in Example 15. In these studies, varied doses of 1 ug, 5 ug, 10 ug, 25 ug, 50 ug, and values in between are used to determine dose response outcomes. Split dosing for a 100 ug total dose includes three or six doses of 1.6 ug, 4.2 ug, 8.3 ug, 16.6 ug, or values and total doses equal to administration of the total dose selected.

Injection sites are chosen from the limbs or any body surface presenting enough area suitable for injection. This may also include a selection of injection depth to target the dermis (Intradermal), epidermis (Epidermal), subcutaneous tissue (SC) or muscle (IM). Injection angle will vary based on targeted delivery site with injections targeting the intradermal site to be 10-15 degree angles from the plane of the surface of the skin, between 20-45 degrees from the plane of the surface of the skin for subcutaneous injections and angles of between 60-90 degrees for injections substantially into the muscle. RNAIMAX™

Example 17. Routes of Administration

Further studies were performed to investigate dosing using different routes of administration. Following the protocol outlined in Example 15, 4 mice per group were dosed intramuscularly (I.M.), intravenously (IV) or subcutaneously (S.C.) by the dosing chart outlined in Table 8. Serum was collected 13 hours post injection from all mice, tissue was collected from the site of injection from the intramuscular and subcutaneous group and the spleen, liver and kidneys were collected from the intravenous group. The results from the intramuscular group are show in FIG. 7A and the subcutaneous group results are shown in FIG. 7B.

TABLE 8

Dosing Chart

Group	Treatment	Route	Dose of mmRNA	Total Dose	Dosing Vehicle
1	Lipoplex-human EPO mmRNA	I.M.	4 × 100 ug + 30% Lipoplex	4 × 70 ul	Lipoplex
2	Lipoplex-human EPO mmRNA	I.M.	4 × 100 ug	4 × 70 ul	Buffer
3	Lipoplex-human EPO mmRNA	S.C.	4 × 100 ug + 30% Lipoplex	4 × 70 ul	Lipoplex
4	Lipoplex-human EPO mmRNA	S.C.	4 × 100 ug	4 × 70 ul	Buffer
5	Lipoplex-human EPO mmRNA	I.V.	200 ug + 30% Lipoplex	140 ul	Lipoplex
6	Lipoplexed-Luciferase mmRNA	I.M.	100 ug + 30% Lipoplex	4 × 70 ul	Lipoplex

TABLE 8-continued

Dosing Chart

Group	Treatment	Route	Dose of mmRNA	Total Dose	Dosing Vehicle
7	Lipoplexed-Luciferase mmRNA	I.M.	100 ug	4 × 70 ul	Buffer
8	Lipoplexed-Luciferase mmRNA	S.C.	100 ug + 30% Lipoplex	4 × 70 ul	Lipoplex
9	Lipoplexed-Luciferase mmRNA	S.C.	100 ug	4 × 70 ul	Buffer
10	Lipoplexed-human EPO mmRNA	I.V.	200 ug + 30% Lipoplex	140 ul	Lipoplex
11	Formulation Buffer	I.M.	4x multi dosing	4 × 70 ul	Buffer

Example 18: In Vivo Delivery of Modified mRNA

Modified RNA was delivered to C57/BL6 mice intramuscularly, subcutaneously, or intravenously to evaluate the bio-distribution of modified RNA using luciferase. A formulation buffer used with all delivery methods contained 150 mM sodium chloride, 2 mM calcium chloride, 2 mM Na+-phosphate which included 1.4 mM monobasic sodium phosphate and 0.6 mM of dibasic sodium phosphate, and 0.5 mM ethylenediaminetetraacetic acid (EDTA) was adjusted using sodium hydroxide to reach a final pH of 6.5 before being filtered and sterilized. A 1× concentration was used as the delivery buffer. To create the lipoplexed solution delivered to the mice, in one vial 50 μg of RNA was equilibrated for 10 minutes at room temperature in the delivery buffer and in a second vial 10 μl RNAiMAX™ was equilibrated for 10 minutes at room temperature in the delivery buffer. After equilibrium, the vials were combined and delivery buffer was added to reach a final volume of 100 μl which was then incubated for 20 minutes at room temperature. Luciferin was administered by intraperitoneal injection (IP) at 150 mg/kg to each mouse prior to imaging during the plateau phase of the luciferin exposure curve which was between 15 and 30 minutes. To create luciferin, 1 g of D-luciferin potassium or sodium salt was dissolved in 66.6 ml of distilled phosphate buffer solution (DPBS), not containing Mg2+ or Ca2+, to make a 15 mg/ml solution. The solution was gently mixed and passed through a 0.2 μm syringe filter, before being purged with nitrogen, aliquoted and frozen at −80° C. while being protected from light as much as possible. The solution was thawed using a waterbath if luciferin was not dissolved, gently mixed and kept on ice on the day of dosing.

Whole body images were taken of each mouse 2, 8 and 24 hours after dosing. Tissue images and serum was collected from each mouse 24 hours after dosing. Mice administered doses intravenously had their liver, spleen, kidneys, lungs, heart, peri-renal adipose tissue and thymus imaged. Mice administered doses intramuscularly or subcutaneously had their liver, spleen, kidneys, lungs, peri-renal adipose tissue, and muscle at the injection site. From the whole body images the bioluminescence was measured in photon per second for each route of administration and dosing regimen.

A. Intramuscular Administration

Mice were intramuscularly (I.M.) administered either modified luciferase mRNA (IVT cDNA sequence shown in SEQ ID NO: 10) (Naked-Luc), lipoplexed modified luciferase mRNA (Lipoplex-luc), lipoplexed modified granulocyte colony-stimulating factor (G-CSF) mRNA (mRNA sequence shown in SEQ ID NO: 4; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1) (Lipoplex-Cytokine) or the formation buffer at a single dose of 50 μg of modified RNA in an injection volume of 50 μl for each formulation in the right hind limb and a single dose of 5 μg of modified RNA in an injection volume of 50 μl in the left hind limb. The bioluminescence average for the luciferase expression signals for each group at 2, 8 and 24 hours after dosing are shown in FIG. **8**A for the left hind limb and FIG. **8**B for the right hind limb. The bioluminescence showed a positive signal at the injection site of the 5 μg and 50 μg modified RNA formulations containing and not containing lipoplex.

B. Subcutaneous Administration

Mice were subcutaneously (S.C.) administered either modified luciferase mRNA (Naked-Luc), lipoplexed modified luciferase mRNA (Lipoplex-luc), lipoplexed modified G-CSF mRNA (Lipoplex-G-CSF) or the formation buffer at a single dose of 50 μg of modified mRNA in an injection volume of 100 μl for each formulation. The bioluminescence average for the luciferase expression signals for each group at 2, 8 and 24 hours after dosing are shown in FIG. **8**C. The bioluminescence showed a positive signal at the injection site of the 50 μg modified mRNA formulations containing and not containing lipoplex.

C. Intravenous Administration

Mice were intravenously (I.V.) administered either modified luciferase mRNA (Naked-Luc), lipoplexed modified luciferase mRNA (Lipoplex-luc), lipoplexed modified G-CSF mRNA (Lipoplex-G-CSF) or the formation buffer at a single dose of 50 μg of modified mRNA in an injection volume of 100 μl for each formulation. The bioluminescence average for the luciferase expression signal in the spleen from each group at 2 hours after dosing is shown in FIG. **8**D. The bioluminescence showed a positive signal in the spleen of the 50 μg modified mRNA formulations containing lipoplex.

Example 19: In Vivo Delivery Using Lipoplexes

A. Human EPO Modified RNA Lipoplex

A formulation containing 100 μg of modified human erythropoietin mRNA (mRNA sequence shown in SEQ ID NO: 7; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1) (EPO; fully modified 5-methylcytosine; N1-methylpseudouridine) was lipoplexed with 30% by volume of RNAIMAX™ (Lipoplex-h-Epo-46; Generation 2 or Gen2) in 50-70 uL delivered intramuscularly to four C57/BL6 mice. Other groups consisted of mice receiving an injection of the lipoplexed modified luciferase mRNA (Lipoplex-luc) (IVT cDNA sequence shown in SEQ ID NO: 10) which served as a control containing 100 μg of modified luciferase mRNA was lipoplexed with 30% by volume of RNAIMAX™ or mice receiving an injection of the formulation buffer as negative control at a dose volume of 65 ul. 13 hours after the intramuscular injection, serum was collected from each mouse to measure the amount of

human EPO protein in the mouse serum by human EPO ELISA and the results are shown in FIG. **9**.

B. Human G-CSF Modified RNA Lipoplex

A formulation containing 100 μg of one of the two types of modified human G-CSF mRNA (mRNA sequence shown in SEQ ID NO: 4; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1) (G-CSF fully modified with 5-methylcytosine and pseudouridine (G-CSF) or G-CSF fully modified with 5-methylcytosine and N1-methyl-pseudouridine (G-CSF-N1) lipoplexed with 30% by volume of RNAIMAX™ and delivered in 150 uL intramuscularly (I.M), in 150 uL subcutaneously (S.C) and in 225 uL intravenously (I.V) to C57/BL6 mice. Three control groups were administered either 100 μg of modified luciferase mRNA (IVT cDNA sequence shown in SEQ ID NO: 10) intramuscularly (Luc-unsp I.M.) or 150 μg of modified luciferase mRNA intravenously (Luc-unsp I.V.) or 150 uL of the formulation buffer intramuscularly (Buffer I.M.). 6 hours after administration of a formulation, serum was collected from each mouse to measure the amount of human G-CSF protein in the mouse serum by human G-CSF ELISA and the results are shown in FIG. **10**.

C. Human G-CSF Modified RNA Lipoplex Comparison

A formulation containing 100 μg of either modified human G-CSF mRNA lipoplexed with 30% by volume of RNAIMAX™ with a 5-methylcytosine (5mc) and a pseudouridine (ψ) modification (G-CSF-Gen1-Lipoplex), modified human G-CSF mRNA with a 5mc and ψ modification in saline (G-CSF-Gen1-Saline), modified human G-CSF mRNA with a N1-5-methylcytosine (N1-5mc) and a ψ modification lipoplexed with 30% by volume of RNAIMAX™ (G-CSF-Gen2-Lipoplex), modified human G-CSF mRNA with a N1-5mc and ψ modification in saline (G-CSF-Gen2-Saline), modified luciferase with a 5mc and ψ modification lipoplexed with 30% by volume of RNAIMAX™ (Luc-Lipoplex), or modified luciferase mRNA with a 5mc and ψ modification in saline (Luc-Saline) was delivered intramuscularly (I.M.) or subcutaneously (S.C.) and a control group for each method of administration was giving a dose of 80 uL of the formulation buffer (F. Buffer) to C57/BL6 mice. 13 hours post injection serum and tissue from the site of injection were collected from each mouse and analyzed by G-CSF ELISA to compare human G-CSF protein levels. The results of the human G-CSF protein in mouse serum from the intramuscular administration are shown in FIG. **11**A, and the subcutaneous administration results are shown in FIG. **11**B.

D. mCherry Modified RNA Lipoplex Comparison

Intramuscular and Subcutaneous Administration

A formulation containing 100 μg of either modified mCherry mRNA (mRNA sequence shown in SEQ ID NO: 5; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1) lipoplexed with 30% by volume of RNAIMAX™ or modified mCherry mRNA in saline is delivered intramuscularly and subcutaneously to mice. A formulation buffer is also administered to a control group of mice either intramuscularly or subcutaneously. The site of injection on the mice may be collected 17 hours post injection for sectioning to determine the cell type(s) responsible for producing protein.

Intravitreal Administration

A formulation containing 10 μg of either modified mCherry mRNA lipoplexed with RNAIMAX™, modified mCherry mRNA in a formulation buffer, modified luciferase mRNA lipoplexed with RNAMAX™, modified luciferase mRNA in a formulation buffer can be administered by intravitreal injection (IVT) in rats in a dose volume of 5 μl/eye. A formulation buffer is also administered by IVT to a control group of rats in a dose volume of 5 μl/eye. Eyes from treated rats can be collected after 18 hours post injection for sectioning and lysating to determine whether mmRNA can be effectively delivered in vivo to the eye and result in protein production, and to also determine the cell type(s) responsible for producing protein in vivo.

Intranasal Administration

A formulation containing 100 μg of either modified mCherry mRNA lipoplexed with 30% by volume of RNAIMAX™, modified mCherry mRNA in saline, modified luciferase mRNA lipoplexed with 30% by volume of RNAIMAX™ or modified luciferase mRNA in saline is delivered intranasally. A formulation buffer is also administered to a control group intranasally. Lungs may be collected about 13 hours post instillation for sectioning (for those receiving mCherry mRNA) or homogenization (for those receiving luciferase mRNA). These samples will be used to determine whether mmRNA can be effectively delivered in vivo to the lungs and result in protein production, and to also determine the cell type(s) responsible for producing protein in vivo.

Example 20: In Vivo Delivery Using Varying Lipid Ratios

Modified mRNA was delivered to C57/BL6 mice to evaluate varying lipid ratios and the resulting protein expression. Formulations of 100 μg modified human EPO mRNA (mRNA sequence shown in SEQ ID NO: 7; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1) lipoplexed with 10%, 30% or 50% RNAIMAX™, 100 μg modified luciferase mRNA (IVT cDNA sequence shown in SEQ ID NO: 10) lipoplexed with 10%, 30% or 50% RNAIMAX™ or a formulation buffer were administered intramuscularly to mice in a single 70 μl dose. Serum was collected 13 hours post injection to undergo a human EPO ELISA to determine the human EPO protein level in each mouse. The results of the human EPO ELISA, shown in FIG. **12**, show that modified human EPO expressed in the muscle is secreted into the serum for each of the different percentage of RNAIMAX™.

Example 21: Intramuscular and Subcutaneous In Vivo Delivery in Mammals

Modified human EPO mRNA (mRNA sequence shown in SEQ ID NO: 7; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1) formulated in saline was delivered to either C57/BL6 mice or Sprague-Dawley rats to evaluate the dose dependency on human EPO production. Rats were intramuscularly injected with 50 μl of the modified human EPO mRNA (h-EPO), modified luciferase mRNA (Luc) (IVT cDNA sequence shown in SEQ ID NO: 10) or the formulation buffer (F.Buffer) as described in the dosing chart Table 9.

Mice were intramuscularly or subcutaneously injected with 50 μl of the modified human EPO mRNA (h-EPO), modified luciferase mRNA (Luc) or the formulation buffer (F.Buffer) as described in the dosing chart Table 10. 13 hours post injection blood was collected and serum was analyzed to determine the amount human EPO for each mouse or rat. The average and geometric mean in pg/ml for the rat study are also shown in Table 9.

TABLE 9

Rat Study

	Group	Dose	R#1	R#2	R#3	R#4	R#5	R#6	Avg. pg/ml	Geometric-mean pg/ml
h-EPO	G#1	150 μg	61.8	86.3	69.9	55.2	59	74.2	67.7	67.1
h-EPO	G#2	100 μg	69.4	77.8	48.2	17.6	101.9	161.5	79.4	66.9
h-EPO	G#3	50 μg	143.6	60.9	173.4	145.9	61.5	23.9	101.5	85.4
h-EPO	G#4	10 μg	7.8	11.8	30.9	36.2	40.6	150.3	46.3	31.2
h-EPO	G#5	1 μg	9.1	35.8	—	46.2	18.1	34.1	28.7	25.4
Luc	G#6	100 μg	34.1	36.5	13.5	13.7	—	—	24.5	22.4
F. Buffer	G#7	—	14.7	18.5	21.2	20.3	—	—	18.7	18.5

TABLE 10

Mouse Study

Route	Treatment	Group	Dose	Average Level in serum pg/ml
IM	h-EPO	1	100 μg	96.2
IM	h-EPO	2	50 μg	63.5
IM	h-EPO	3	25 μg	18.7
IM	h-EPO	4	10 μg	25.9
IM	h-EPO	5	1 μg	2.6
IM	Luc	6	100 μg	0
IM	F. Buffer	7	—	1.0
SC	h-EPO	1	100 μg	72.0
SC	Luc	2	100 μg	26.7
SC	F. Buffer	3	—	17.4

Example 22: Duration of Activity after Intramuscular In Vivo Delivery in Rats

Modified human EPO mRNA (mRNA sequence shown in SEQ ID NO: 7; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1) formulated in saline was delivered to Sprague-Dawley rats to determine the duration of the dose response. Rats were intramuscularly injected with 50 μl of the modified human EPO mRNA (h-EPO), modified luciferase mRNA (IVT cDNA sequence shown in SEQ ID NO: 10) (Luc) or the formulation buffer (F.Buffer) as described in the dosing chart Table 11. The rats were bled 2, 6, 12, 24, 48 and 72 hours after the intramuscular injection to determine the concentration of human EPO in serum at a given time. The average and geometric mean in pg/ml for this study are also shown in Table 11.

Example 23. In Vitro Transfection of VEGF-A

Human vascular endothelial growth factor-isoform A (VEGF-A) modified mRNA (mRNA sequence shown in SEQ ID NO: 12; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1) was transfected via reverse transfection in Human Keratinocyte cells in 24 multi-well plates. Human Keratinocytes cells were grown in EPILIFE® medium with Supplement S7 from Invitrogen (Carlsbad, Calif.) until they reached a confluence of 50-70%. The cells were transfected with 0, 46.875, 93.75, 187.5, 375, 750, and 1500 ng of modified mRNA (mmRNA) encoding VEGF-A which had been complexed with RNAIMAX™ from Invitrogen (Carlsbad, Calif.). The RNA: RNAIMAX™ complex was formed by first incubating the RNA with Supplement-free EPILIFE® media in a 5× volumetric dilution for 10 minutes at room temperature. In a second vial, RNAIMAX™ reagent was incubated with Supplement-free EPILIFE® Media in a 10× volumetric dilution for 10 minutes at room temperature. The RNA vial was then mixed with the RNAIMAX™ vial and incubated for 20-30 minutes at room temperature before being added to the cells in a drop-wise fashion.

The fully optimized mRNA encoding VEGF-A transfected with the Human Keratinocyte cells included modifications during translation such as natural nucleoside triphosphates (NTP), pseudouridine at each uridine site and 5-methylcytosine at each cytosine site (pseudo-U/5mC), and N1-methyl-pseudouridine at each uridine site and 5-methylcytosine at each cytosine site (N1-methyl-Pseudo-U/5mC). Cells were transfected with the mmRNA encoding VEGF-A and secreted VEGF-A concentration (pg/ml) in the culture medium was measured at 6, 12, 24, and 48 hours post-transfection for each of the concentrations using an ELISA kit from Invitrogen (Carlsbad, Calif.) following the

TABLE 11

Dosing Chart

	Group	Dose	R#1	R#2	R#3	R#4	R#5	R#6	R#7	Avg. pg/ml	Geometric-mean pg/ml
h-EPO	2 hour	100 μg	60.0	62.4	53.6	33.2	68.6	66.4	72.8	59.6	58.2
h-EPO	6 hour	100 μg	66.4	102.5	45.6	78.1	56.8	122.5	8.1	68.6	55.8
h-EPO	12 hour	100 μg	132.9	55.1	89.0	80.1	85.6	105.6	63.3	87.4	84.5
h-EPO	24 hour	100 μg	51.1	76.3	264.3	142.4	77.6	73.5	75.0	108.6	95.3
h-EPO	48 hour	100 μg	96.3	59.0	85.7	82.6	63.5	80.3	—	77.9	77.0
h-EPO	72 hour	100 μg	46.3	66.9	73.5	57.3	136.7	110	69.7	80.1	75.8
Luc	24, 48 and 72 hour	100 μg	60.2	38.5	48.8	46.1	3.6	26.1	—	37.2	29.2
F. Buffer	24, 48 and 72 hour	—	50.0	10.0	80.9	54.7	—	—	—	48.9	10.4

manufacturers recommended instructions. These data, shown in Table 12, show that modified mRNA encoding VEGF-A is capable of being translated in Human Keratinocyte cells and that VEGF-A is transported out of the cells and released into the extracellular environment.

TABLE 12

VEGF-A Dosing and Protein Secretion

Dose (ng)	6 hours (pg/ml)	12 hours (pg/ml)	24 hours (pg/ml)	48 hours (pg/ml)
VEGF-A Dose Containing Natural NTPs				
46.875	10.37	18.07	33.90	67.02
93.75	9.79	20.54	41.95	65.75
187.5	14.07	24.56	45.25	64.39
375	19.16	37.53	53.61	88.28
750	21.51	38.90	51.44	61.79
1500	36.11	61.90	76.70	86.54
VEGF-A Dose Containing Pseudo-U/5mC				
46.875	10.13	16.67	33.99	72.88
93.75	11.00	20.00	46.47	145.61
187.5	16.04	34.07	83.00	120.77
375	69.15	188.10	448.50	392.44
750	133.95	304.30	524.02	526.58
1500	198.96	345.65	426.97	505.41
VEGF-A Dose Containing N1-methyl-Pseudo-U/5mC				
46.875	0.03	6.02	27.65	100.42
93.75	12.37	46.38	121.23	167.56
187.5	104.55	365.71	1025.41	1056.91
375	605.89	1201.23	1653.63	1889.23
750	445.41	1036.45	1522.86	1954.81
1500	261.61	714.68	1053.12	1513.39

Example 24. In Vivo Studies of Factor IX

Human Factor IX mmRNA (mRNA shown in SEQ ID NO: 8; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1) (Gen1; fully modified 5-methylcytosine and pseudouridine) formulated in saline was delivered to mice via intramuscular injection. The results demonstrate that Factor IX protein was elevated in serum as measured 13 hours after administration.

In this study, mice (N=5 for Factor IX, N=3 for Luciferase or Buffer controls) were intramuscularly injected with 50 μl of the Factor IX mmRNA (mRNA sequence shown in SEQ ID NO: 8; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1), Luciferase (cDNA sequence for IVT shown in SEQ ID NO: 10) or the formulation buffer (F.Buffer) at 2×100 ug/mouse. The mice were bled at 13 hours after the intramuscular injection to determine the concentration of human the polypeptide in serum in pg/mL. The results revealed that administration of Factor IX mmRNA resulted in levels of 1600 pg/mL at 13 hours as compared to less than 100 pg/mL of Factor IX for either Luciferase or buffer control administration.

Example 25. Multi-Site Administration: Intramuscular and Subcutaneous

Human G-CSF mmRNA (mRNA sequence shown in SEQ ID NO: 4; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1) modified as either Gen1 or Gen2 (5-methylcytosine (5mc) and a pseudouridine (ψ) modification, G-CSF-Gen1; or N1-5-methylcytosine (N1-5mc) and a ψ modification, G-CSF-Gen2) and formulated in saline were delivered to mice via intramuscular (IM) or subcutaneous (SC) injection. Injection of four doses or 2×50 ug (two sites) daily for three days (24 hrs interval) was performed. The fourth dose was administered 6 hrs before blood collection and CBC analysis. Controls included Luciferase (cDNA sequence for IVT shown in SEQ ID NO: 10) or the formulation buffer (F.Buffer). The mice were bled at 72 hours after the first mmRNA injection (6 hours after the last mmRNA dose) to determine the effect of mmRNA-encoded human G-CSF on the neutrophil count. The dosing regimen is shown in Table 13 as are the resulting neutrophil counts (thousands/uL). Asterisks indicate statistical significance at $p<0.05$.

For intramuscular administration, the data reveal a four fold increase in neutrophil count above control at day 3 for the Gen1 G-CSF mmRNA and a two fold increase for the Gen2 G-CSF mmRNA. For subcutaneous administration, the data reveal a two fold increase in neutrophil count above control at day 3 for the Gen2 CT-CSF mmRNA

TABLE 13

Dosing Regimen

Gr.	Treatment	Route	N =	Dose (μg/mouse)	Dose Vol. (μl/mouse)	Dosing Vehicle	Neutrophil Thous/uL
1	G-CSF (Gen1)	I.M	5	2 × 50 ug (four doses)	50	F. buffer	840*
2	G-CSF (Gen1)	S.C	5	2 × 50 ug (four doses)	50	F. buffer	430
3	G-CSF (Gen2)	I.M	5	2 × 50 ug (four doses)	50	F. buffer	746*
4	G-CSF (Gen2)	S.C	5	2 × 50 ug (four doses)	50	F. buffer	683
5	Luc (Gen1)	I.M.	5	2 × 50 ug (four doses)	50	F. buffer	201
6	Luc (Gen1)	S.C.	5	2 × 50 ug (four doses)	50	F. buffer	307
7	Luc (Gen2)	I.M	5	2 × 50 ug (four doses)	50	F. buffer	336
8	Luc (Gen2)	S.C	5	2 × 50 ug (four doses)	50	F. buffer	357
9	F. Buffer	I.M	4	0 (four doses)	50	F. buffer	245
10	F. Buffer	S.C.	4	0 (four doses)	50	F. buffer	509
11	Untreated	—	4			—	312

Example 26. Intravenous Administration

Human G-CSF mmRNA (mRNA sequence shown in SEQ ID NO: 4; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1) modified with 5-methylcytosine (5mc) and a pseudouridine (ψ) modification; or having no modifications and formulated in 10% lipoplex (RNAIMAX™) were delivered to mice at a dose of 50 ug RNA and in a volume of 100 ul via intravenous (IV) injection at days 0, 2 and 4. Neutrophils were measured at days 1, 5 and 8. Controls included non-specific mammalian

RNA or the formulation buffer alone (F.Buffer). The mice were bled at days 1, 5 and 8 to determine the effect of mmRNA-encoded human G-CSF to increase neutrophil count. The dosing regimen is shown in Table 14 as are the resulting neutrophil counts (thousands/uL; K/uL).

For intravenous administration, the data reveal a four to five fold increase in neutrophil count above control at day 5 with G-CSF mmRNA but not with unmodified G-CSF mRNA or non-specific controls. Blood count returned to baseline four days after the final injection. No other changes in leukocyte populations were observed.

An asterisk indicates statistical significance at $p<0.001$ compared to buffer.

TABLE 14

Dosing Regimen

Gr.	Treatment	N =	Dose Vol. (µl/mouse)	Dosing Vehicle	Neutrophil K/uL
1	G-CSF (Gen1) Day 1	5	100	10% lipoplex	2.91
2	G-CSF (Gen1) Day 5	5	100	10% lipoplex	5.32*
3	G-CSF (Gen1) Day 8	5	100	10% lipoplex	2.06
4	G-CSF (no modification) Day 1	5	100	10% lipoplex	1.88
5	G-CSF (no modification) Day 5	5	100	10% lipoplex	1.95
6	G-CSF (no modification) Day 8	5	100	10% lipoplex	2.09
7	RNA Control Day 1	5	100	10% lipoplex	2.90
8	RNA Control Day 5	5	100	10% lipoplex	1.68
9	RNA Control Day 8	4	100	10% lipoplex	1.72
10	F. Buffer Day 1	4	100	10% lipoplex	2.51
11	F. Buffer Day 5	4	100	10% lipoplex	1.31
12	F. Buffer Day 8	4	100	10% lipoplex	1.92

Example 27. Saline Formulation: Intramuscular Administration

Human G-CSF mmRNA (mRNA sequence shown in SEQ ID NO: 4; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1) and human EPO mmRNA (mRNA sequence shown in SEQ ID NO: 7; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1); G-CSF mmRNA (modified with 5-methylcytosine (5mc) and pseudouridine (ψ)) and EPO mmRNA (modified with N1-5-methylcytosine (N1-5mc) and ψ modification), were formulated in saline and delivered to mice via intramuscular (IM) injection at a dose of 100 ug.

Controls included Luciferase (IVT cDNA sequence shown in SEQ ID NO: 10) or the formulation buffer (F.Buffer). The mice were bled at 13 hours after the injection to determine the concentration of the human polypeptide in serum in pg/mL (G-CSF groups measured human G-CSF in mouse serum and EPO groups measured human EPO in mouse serum). The data are shown in Table 15.

TABLE 15

Dosing Regimen

Group	Treatment	N =	Dose Vol. (µl/mouse)	Dosing Vehicle	Average Protein Product pg/mL, serum
G-CSF	G-CSF	5	50	Saline	19.8
G-CSF	Luciferase	5	50	Saline	0.5
G-CSF	F. buffer	5	50	F. buffer	0.5
EPO	EPO	5	50	Saline	191.5
EPO	Luciferase	5	50	Saline	15.0
EPO	F. buffer			F. buffer	4.8

Example 28. EPO Multi-Dose/Multi-Administration

Studies utilizing multiple intramuscular injection sites at one time point were designed and performed.

The design of a single multi-dose experiment involved using human erythropoietin (EPO) mmRNA (mRNA sequence shown in SEQ ID NO: 7; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1) or G-CSF (mRNA sequence shown in SEQ ID NO: 4; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1) administered in saline. The dosing vehicle (F. buffer) was used as a control. The EPO and G-CSF mmRNA were modified with 5-methylcytosine at each cytosine and pseudouridine replacement at each uridine site.

Animals (n=5), Sprague-Dawley rats, were injected IM (intramuscular) for the single unit dose of 100 ug (delivered to one thigh). For multi-dosing 6 doses of 100 ug (delivered to two thighs) were used for both EPO and G-CSF mmRNA. Control dosing involved use of buffer at a single dose. Human EPO blood levels were evaluated 13 hours post injection.

Human EPO protein was measured in rat serum 13 hours post I.M. Five groups of rats were treated and evaluated. The results are shown in Table 16.

TABLE 16

Multi-dose study

Group	Treatment	Dose of mmRNA	Total Dose	Avg. Pg/mL human EPO, serum
1	Human EPO mmRNA	1 × 100 ug	100 ug	143
2	Human EPO mmRNA	6 × 100 ug	600 ug	256
3	G-CSF mmRNA	1 × 100 ug	100 ug	43
4	G-CSF mmRNA	6 × 100 ug	600 ug	58
5	Buffer Alone	—	—	20

Example 29. Signal Sequence Exchange Study

Several variants of mmRNAs encoding human Granulocyte colony stimulating factor (G-CSF) (mRNA sequence shown in SEQ ID NO: 4; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1) were synthesized using modified nucleotides pseudouridine and 5-methylcytosine (pseudo-U/5mC). These variants included the G-CSF constructs encoding either the wild-type N terminal secretory signal peptide sequence (MAGPATQSPMKLMALQLLLWHSALWTVQEA; SEQ

ID NO: 13), no secretory signal peptide sequence, or secretory signal peptide sequences taken from other mRNAs. These included sequences where the wild type GCSF signal peptide sequence was replaced with the signal peptide sequence of either: human α-1-anti trypsin (MMPSSVSWGILLLAGLCCLVPVSLA; SEQ ID NO: 14), human Factor IX (MQRVNMIMAESPSLITICLLGYLLSAECTVFLDHENANKILNRPKR; SEQ ID NO: 15), human Prolactin (MKGSLLLLLVSNLLLCQSVAP; SEQ ID NO: 16), or human Albumin (MKWVTFISLLFLFSSAYSRGVFRR; SEQ ID NO: 17).

250 ng of modified mRNA encoding each G-CSF variant was transfected into HEK293A (293A in the table), mouse myoblast (MM in the table) (C2C12, CRL-1772, ATCC) and rat myoblast (RM in the table) (L6 line, CRL-1458, ATCC) cell lines in a 24 well plate using 1 ul of Lipofectamine 2000 (Life Technologies), each well containing 300,000 cells. The supernatants were harvested after 24 hrs and the secreted G-CSF protein was analyzed by ELISA using the Human G-CSF ELISA kit (Life Technologies). The data shown in Table 17 reveal that cells transfected with G-CSF mmRNA encoding the Albumin signal peptide secrete at least 12 fold more G-CSF protein than its wild type counterpart.

TABLE 17

Signal Peptide Exchange

Signal peptides	293A (pg/ml)	MM (pg/ml)	RM (pg/ml)
G-CSF Natural	9650	3450	6050
α-1-anti trypsin	9950	5000	8475
Factor IX	11675	6175	11675
Prolactin	7875	1525	9800
Albumin	122050	81050	173300
No Signal peptide	0	0	0

Example 30. Cytokine Study: PBMC

PBMC Isolation and Culture:

50 mL of human blood from two donors was received from Research Blood Components (lots KP30928 and KP30931) in sodium heparin tubes. For each donor, the blood was pooled and diluted to 70 mL with DPBS (SAFC Bioscience 59331C, lot 071M8408) and split evenly between two 50 mL conical tubes. 10 mL of Ficoll Paque (GE Healthcare 17-5442-03, lot 10074400) was gently dispensed below the blood layer. The tubes were centrifuged at 2000 rpm for 30 minutes with low acceleration and braking. The tubes were removed and the buffy coat PMBC layers were gently transferred to a fresh 50 mL conical and washed with DPBS. The tubes were centrifuged at 1450 rpm for 10 minutes.

The supernatant was aspirated and the PBMC pellets were resuspended and washed in 50 mL of DPBS. The tubes were centrifuged at 1250 rpm for 10 minutes. This wash step was repeated, and the PBMC pellets were resuspended in 19 mL of Optimem I (Gibco 11058, lot 1072088) and counted. The cell suspensions were adjusted to a concentration of 3.0× 10^6 cells/mL live cells.

These cells were then plated on five 96 well tissue culture treated round bottom plates (Costar 3799) per donor at 50 uL per well. Within 30 minutes, transfection mixtures were added to each well at a volume of 50 uL per well. After 4 hours post transfection, the media was supplemented with 10 uL of Fetal Bovine Serum (Gibco 10082, lot 1012368)

Transfection Preparation:

mmRNA encoding human G-CSF (mRNA sequence shown in SEQ ID NO: 4; poly-A tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap1) (containing either (1) natural NTPs, (2) 100% substitution with 5-methyl cytidine and pseudouridine, or (3) 100% substitution with 5-methyl cytidine and N1-methyl pseudouridine; mmRNA encoding luciferase (IVT cDNA sequence shown in SEQ ID NO: 10) (containing either (1) natural NTPs or (2) 100% substitution with 5-methyl cytidine and pseudouridine) and TLR agonist R848 (Invivogen tlrl-r848) were diluted to 38.4 ng/uL in a final volume of 2500 uL Optimem I.

Separately, 432 uL of Lipofectamine 2000 (Invitrogen 11668-027, lot 1070962) was diluted with 13.1 mL Optimem I. In a 96 well plate nine aliquots of 135 uL of each mmRNA, positive control (R-848) or negative control (Optimem I) was added to 135 uL of the diluted Lipofectamine 2000. The plate containing the material to be transfected was incubated for 20 minutes. The transfection mixtures were then transferred to each of the human PBMC plates at 50 uL per well. The plates were then incubated at 37 C. At 2, 4, 8, 20, and 44 hours each plate was removed from the incubator, and the supernatants were frozen.

After the last plate was removed, the supernatants were assayed using a human G-CSF ELISA kit (Invitrogen KHC2032) and human IFN-alpha ELISA kit (Thermo Scientific 41105-2). Each condition was done in duplicate.

Results:

The ability of unmodified and modified mRNA (mmRNAs) to produce the encoded protein was assessed (G-CSF production) over time as was the ability of the mRNA to trigger innate immune recognition as measured by interferon-alpha production. Use of in vitro PBMC cultures is an accepted way to measure the immunostimulatory potential of oligonucleotides (Robbins et al., Oligonucleotides 2009 19:89-102).

Results were interpolated against the standard curve of each ELISA plate using a four parameter logistic curve fit. Shown in Tables 18 and 19 are the average from 2 separate PBMC donors of the G-CSF and IFN-alpha production over time as measured by specific ELISA.

In the G-CSF ELISA, background signal from the Lipofectamine 2000 untreated condition was subtracted at each timepoint. The data demonstrated specific production of human G-CSF protein by human peripheral blood mononuclear is seen with G-CSF mRNA containing natural NTPs, 100% substitution with 5-methyl cytidine and pseudouridine, or 100% substitution with 5-methyl cytidine and N1-methyl pseudouridine. Production of G-CSF was significantly increased through the use of modified mRNA relative to unmodified mRNA, with the 5-methyl cytidine and N1-methyl pseudouridine containing G-CSF mmRNA showing the highest level of G-CSF production. With regards to innate immune recognition, unmodified mRNA resulted in substantial IFN-alpha production, while the modified mRNA largely prevented interferon-alpha production.

TABLE 18

G-CSF Signal
G-CSF signal - 2 Donor Average

pg/mL	2 Hr	4 Hr	8 Hr	20 Hr	44 Hr
G-CSF (5mC/pseudouridine)	120.3	136.8	421.0	346.1	431.8
G-CSF (5mC/N1-methyl pseudouridine)	256.3	273.7	919.3	1603.3	1843.3
GCSF (Natural-no modification)	63.5	92.6	129.6	258.3	242.4
Luciferase (5mC/pseudouridine)	4.5	153.7	33.0	186.5	58.0

TABLE 19

IFN-alpha signal
IFN-alpha signal - 2 donor average

pg/mL	2 Hr	4 Hr	8 Hr	20 Hr	44 Hr
G-CSF (5mC/pseudouridine)	21.1	2.9	3.7	22.7	4.3
G-CSF (5mC/N1-methyl pseudouridine)	0.5	0.4	3.0	2.3	2.1
G-CSF (Natural)	0.0	2.1	23.3	74.9	119.7
Luciferase (5mC/pseudouridine)	0.4	0.4	4.7	1.0	2.4
R-848	39.1	151.3	278.4	362.2	208.1
Lipofectamine 2000 control	0.8	17.2	16.5	0.7	3.1

Example 31. Quantification in Exosomes

The quantity and localization of the mmRNA of the present invention can be determined by measuring the amounts (initial, timecourse, or residual basis) in isolated exosomes. In this study, since the mmRNA are typically codon-optimized and distinct in sequence from endogenous mRNA, the levels of mmRNA are quantitated as compared to endogenous levels of native or wild type mRNA by using the methods of Gibbings, PCT/IB2009/005878, the contents of which are incorporated herein by reference in their entirety.

In these studies, the method is performed by first isolating exosomes or vesicles preferably from a bodily fluid of a patient previously treated with a polynucleotide, primary construct or mmRNA of the invention, then measuring, in said exosomes, the polynucleotide, primary construct or mmRNA levels by one of mRNA microarray, qRT-PCR, or other means for measuring RNA in the art including by suitable antibody or immunohistochemical methods.

Example 32: Bifunctional mmRNA

Using the teachings and synthesis methods described herein, modified RNAs are designed and synthesized to be bifunctional, thereby encoding one or more cytotoxic protein molecules as well as be synthesized using cytotoxic nucleosides.

Administration of the bifunctional modified mRNAs is effected using either saline or a lipid carrier. Once administered, the bifunctional modified mRNA is translated to produce the encoded cytotoxic peptide. Upon degradation of the delivered modified mRNA, the cytotoxic nucleosides are released which also effect therapeutic benefit to the subject.

Example 33. Synthesis of Modified mRNA

Modified mRNA is generated from a cDNA template containing a T7 RNA-polymerase promoter sequence using a commercially available T7 RNA polymerase transcription kit (MEGASCRIPT® High Yield Transcription KIT, AMBION®, Austin, Tex.; MSCRIPT™ mRNA Production Kit, EPICENTRE® Biotechnologies, Madison, Wis.). An in vitro transcription reaction contains between 1-2 μg of template DNA in the form of a linearized plasmid, PCR product, or single-stranded oligonucleotide with a double-stranded polymerase promoter region. The template DNA encodes a strong translation initiation sequence such as a strong consensus Kozak sequence or an optimized, high-expression IRES including the EMCV IRES. Reaction volumes are between 20-40 μl and contain 3'-O-Me-m^7-G(5')ppp(5')G ARCA cap analog (NEW ENGLAND BIOLABS®) in addition to an optimized ribonucleotide mixture of determined modified adenine, guanine, cytidine and uridine ribonucleotide analogs. Final reaction concentrations for nucleotide are 6 mM for the cap analog and 1.5-7.5 mM for each of the other nucleotides. The temperature and duration of the in vitro transcription reaction are optimized for efficiency, fidelity and yield. Reactions may be incubated from 3-6 hours and up to 16 hours at 37° C. Following the in vitro transcription reaction, the capped mRNA undergoes polyadenylation using a commercially available poly-A tailing kit (EPICENTRE® Biotechnologies, Madison, Wis.). The resulting capped and polyadenylated synthetic mRNA is then purified by denaturing agarose gel electrophoresis to confirm production of full-length product and to remove any degradation products followed by spin column filtration (RNeasy Kit, Qiagen, Valencia, Calif.; MEGACLEAR™ AMBION®, Austin, Tex.). Purified synthetic mRNAs are resuspended in RNase-free water containing an RNase inhibitor (RNASIN® Plus RNase Inhibitor, Promega, Madison, Wis.), quantified by NANODROP™ (Thermo Scientific, Logan, Utah) and stored at −20° C.

Example 34: Bulk Transfection of Modified mRNA into Cell Culture

A. Cationic Lipid Delivery Vehicles

RNA transfections are carried out using RNAIMax (Invitrogen, Carlsbad, Calif.) or TRANSIT-mRNA (Mirus Bio, Madison, Wis.) cationic lipid delivery vehicles. RNA and reagent are first diluted in Opti-MEM basal media (Invitrogen, Carlsbad, Calif.). 100 ng/uL RNA is diluted 5× and 5 μL of RNAIMax perm of RNA is diluted 10×. The diluted components are pooled and incubated 15 minutes at room temperature before they are dispensed to culture media. For TRANSIT-mRNA transfections, 100 ng/uL RNA is diluted 10× in Opti-MEM and BOOST reagent is added (at a concentration of 2 μL perm of RNA), TRANSIT-mRNA is added (at a concentration of 2 μL perm of RNA), and then the RNA-lipid complexes are delivered to the culture media after a 2-minute incubation at room temperature. RNA transfections are performed in Nutristem xenofree hES media (STEMGENT®, Cambridge, Mass.) for RiPS derivations, Dermal Cell Basal Medium plus Keratinocyte Growth Kit (ATCC) for keratinocyte experiments, and Opti-MEM plus 2% FBS for all other experiments. Successful introduction of a modified mRNA (mmRNA) into host cells can be monitored using various known methods, such as a fluorescent marker, such as Green Fluorescent Protein (GFP). Successful transfection of a modified mRNA can also be determined by measuring the protein expression level of the target polypeptide by e.g., Western Blotting or immunocytochemistry. Similar methods may be followed for large volume scale-up to multi-liter (5-10,000 L) culture format following similar RNA-lipid complex ratios.

B. Electroporation Delivery of Exogenous Synthetic mRNA Transcripts

Electroporation parameters are optimized by transfecting MRC-5 fibroblasts with in vitro synthetic modified mRNA (mmRNA) transcripts and measuring transfection efficiency by quantitative RT-PCR with primers designed to specifically detect the exogenous transcripts. Discharging a 150 uF capacitor charged to F into 2.5×10^6 cells suspended in 50 μl of Opti-MEM (Invitrogen, Carlsbad, Calif.) in a standard electroporation cuvette with a 2 mm gap is sufficient for repeated delivery in excess of 10,000 copies of modified mRNA transcripts per cell, as determined using the standard curve method, while maintaining high viability (>70%). Further experiments may reveal that the voltage required to efficiently transfect cells with mmRNA transcripts can depend on the cell density during electroporation. Cell density may vary from 1×10^6 cell/50 μl to a density of 2.5×10^6 cells/50 μl and require from 110V to 145V to transfect cells with similar efficiencies measured in transcript copies per cell. Large multi-liter (5-10,000 L) electroporation may be performed similar to large volume flow electroporation strategies similar to methods described with the above described constraints (Li et al., 2002; Geng et al., 2010).

Example 35. Overexpression of Ceramide Transfer Protein to Increase Therapeutic Antibody Protein Production in Established CHO Cell Lines

A. Batch Culture

An antibody producing CHO cell line (CHO DG44) secreting a humanized therapeutic IgG antibody is transfected a single time with lipid cationic delivery agent alone (control) or a synthetic mRNA transcript encoding wild type ceramide transfer protein (CERT) or a non-phosphorylation competent Ser132A CERT mutant. The sequences are taught in for example, U.S. Ser. No. 13/252,049, the contents of which are incorporated herein by reference in their entirety. CERT is an essential cytosolic protein in mammalian cells that transfers the sphingolipid ceramide from the endoplasmic reticulum to the Golgi complex where it is converted to sphingomyelin (Hanada et al., 2003). Overexpression of CERT significantly enhances the transport of secreted proteins to the plasma membrane and improves the production of proteins that are transported via the secretory pathway from eukaryotic cells thereby enhancing secretion of proteins in the culture medium. Synthetic mRNA transcripts are pre-mixed with a lipid cationic delivery agent at a 2-5:1 carrier:RNA ratio. The initial seeding density is about 2×10^5 viable cells/mL. The synthetic mRNA transcript is delivered after initial culture seeding during the exponential culture growth phase to achieve a final synthetic mRNA copy number between 10×10^2 and 10×10^3 per cell. The basal cell culture medium used for all phases of cell inoculum generation and for growth of cultures in bioreactors was modified CD-CHO medium containing glutamine, sodium bicarbonate, insulin and methotrexate. The pH of the medium was adjusted to 7.0 with 1 N HCl or 1N NaOH after addition of all components. Culture run times ended on days 7, 14, 21 or 28+. Production-level 50 L scale reactors (stainless steel reactor with two marine impellers) were used and are scalable to >10,000 L stainless steel reactors (described in commonly-assigned patent application U.S. Ser. No. 60/436,050, filed Dec. 23, 2002, and U.S. Ser. No. 10/740,645). A data acquisition system (Intellution Fix 32, OSIsoft, LLC, San Leandro, Calif.) recorded temperature, pH, and dissolved oxygen (DO) throughout runs. Gas flows were controlled via rotameters. Air was sparged into the reactor via a submerged frit (5 μm pore size) and through the reactor head space for CO_2 removal. Molecular oxygen was sparged through the same frit for DO control. CO_2 was sparged through same frit as used for pH control. Samples of cells were removed from the reactor on a daily basis. A sample used for cell counting was stained with trypan blue (Sigma, St. Louis, Mo.). Cell count and cell viability determination were performed via hemocytometry using a microscope. For analysis of metabolites, additional samples were centrifuged for 20 minutes at 2000 rpm (4° C.) for cell separation. Supernatant was analyzed for the following parameters: titer, sialic acid, glucose, lactate, glutamine, glutamate, pH, pO_2, pCO_2, ammonia, and, optionally, lactate dehydrogenase (LDH). Additional back-up samples were frozen at −20° C. To measure secreted humanized IgG antibody titers, supernatant is taken from seed-stock cultures of all stable cell pools, the IgG titer is determined by ELISA and divided by the mean number of cells to calculate the specific productivity. The highest values are the cell pools with the Ser132A CERT mutant, followed by wild type CERT. In both, IgG expression is markedly enhanced compared to carrier-alone or untransfected cells.

Continuous or Batch-Fed Culture

An antibody producing CHO cell line (CHO DG44) secreting humanized IgG antibody is transfected with lipid cationic delivery agent alone (control) or a synthetic mRNA transcript encoding wild type ceramide transfer protein or a non-phosphorylation competent Ser132A CERT mutant. Synthetic mRNA transcripts are pre-mixed with a lipid cationic delivery agent at a 2-5:1 carrier:RNA ratio. The initial seeding density was about 2×10^5 viable cells/mL. Synthetic mRNA transcript is delivered after initial culture seeding during the exponential culture growth phase to achieve a final synthetic mRNA copy number between 10×10^2 and 10×10^3 per cell. The basal cell culture medium used for all phases of cell inoculum generation and for growth of cultures in bioreactors was modified CD-CHO medium containing glutamine, sodium bicarbonate, insulin and methotrexate. The pH of the medium was adjusted to 7.0 with 1 N HCl or 1N NaOH after addition of all components. Bioreactors of 5 L scale (glass reactor with one marine impeller) were used to obtain maximum CERT protein production and secreted humanized IgG antibody curves. For continuous or fed-batch cultures, the culturing run time is increased by supplementing the culture medium one or more times daily (or continuously) with fresh medium during the run. In the a continuous and fed-batch feeding regimens, the cultures receive feeding medium as a continuously-supplied infusion, or other automated addition to the culture, in a timed, regulated, and/or programmed fashion so as to achieve and maintain the appropriate amount of synthetic mRNA:carrier in the culture. The preferred method is a feeding regimen of a once per day bolus feed with feeding medium containing synthetic mRNA:carrier on each day of the culture run, from the beginning of the culture run to the day of harvesting the cells. The daily feed amount was recorded on batch sheets. Production-level 50 L scale reactors (stainless steel reactor with two marine impellers) were used and are scalable to >10,000 L stainless steel reactors. A data acquisition system (Intellution Fix 32) recorded temperature, pH, and dissolved oxygen (DO) throughout runs. Gas flows were controlled via rotameters. Air was sparged into the reactor via a submerged frit (5 μm pore size) and through the reactor head space for CO_2 removal. Molecular oxygen was sparged through the same frit for DO control. CO_2 was sparged through same frit as

used for pH control. Samples of cells were removed from the reactor on a daily basis. A sample used for cell counting was stained with trypan blue (Sigma, St. Louis, Mo.). Cell count and cell viability determination were performed via hemocytometry using a microscope. For analysis of metabolites, additional samples were centrifuged for 20 minutes at 2000 rpm (4° C.) for cell separation. Supernatant was analyzed for the following parameters: titer, sialic acid, glucose, lactate, glutamine, glutamate, pH, pO_2, pCO_2, ammonia, and, optionally, lactate dehydrogenase (LDH). Additional back-up samples were frozen at −20° C. To measure secreted humanized IgG antibody titers, supernatant is taken from seed-stock cultures of all stable cell pools, the IgG titer is determined by ELISA and divided by the mean number of cells to calculate the specific productivity. The highest values are the cell pools with the Ser132A CERT mutant, followed by wild type CERT. In both, IgG expression is markedly enhanced compared to carrier-alone or untransfected cells.

Example 36. De Novo Generation of a Mammalian Cell Line Expressing Human Erythropoietin as a Therapeutic Agent

A. Batch Culture

This Example describes the production of human erythropoietin protein (EPO) from cultured primary CHO cells. Erythropoietin is a glycoprotein hormone that is required for red blood cell synthesis. EPO protein may be used as a therapeutic agent for anemia from cancer, heart failure, chronic kidney disease and myelodysplasia. Primary CHO cells are isolated and cultured as described (Tjio and Puck, 1958). Primary CHO cells were then expanded in modified CD-CHO medium containing glutamine, sodium bicarbonate, insulin, and methotrexate (see Example 35) using T-75 flasks (Corning, Corning, N.Y.) and 250 and 500 mL spinners (Bellco, Vineland, N.J.). T-flasks and spinners were incubated at 37° C. in 6% CO_2. After sufficient inoculum was generated, the culture was transferred into a either a 5 L or a 50 L bioreactor as described above (see Example 35). Synthetic mRNA transcript encoding the human erythropoietin protein are pre-mixed with a lipid cationic delivery agent at a 2-5:1 carrier:RNA ratio in a minimum of 1% total culture volume. The initial seeding density is about 2×10^5 viable cells/mL. The synthetic mRNA transcript is delivered after initial culture seeding during the exponential culture growth phase to achieve a final synthetic mRNA copy number between 10×10^2 and 10×10^3 per cell. Culture growth and analysis were performed as described above (see Example 34).

B. Continuous or Batch-Fed Culture

A primary CHO cell line derived and expanded as described above (see Example 36a) is transfected with lipid cationic delivery agent alone (control) or a synthetic mRNA transcript encoding human erythropoietin protein. Synthetic mRNA transcripts are pre-mixed with a lipid cationic delivery agent at a 2-5:1 carrier:RNA ratio. The initial seeding density was about 2×10^5 viable cells/mL. Synthetic mRNA transcript is delivered after initial culture seeding during the exponential culture growth phase to achieve a final synthetic mRNA copy number between 10×10^2 and 10×10^3 per cell. Culture conditions were as described above (Example 35a). For continuous or fed-batch cultures, the culturing run time is increased by supplementing the culture medium one or more times daily (or continuously) with fresh medium during the run. In the a continuous and fed-batch feeding regimens, the cultures receive feeding medium as a continuously-supplied infusion, or other automated addition to the culture, in a timed, regulated, and/or programmed fashion so as to achieve and maintain the appropriate amount of synthetic mRNA:carrier in the culture. The preferred method is a feeding regimen of a once per day bolus feed with feeding medium containing synthetic mRNA:carrier on each day of the culture run, from the beginning of the culture run to the day of harvesting the cells. The daily feed amount was recorded on batch sheets. Production-level 50 L scale reactors (stainless steel reactor with two marine impellers) were used and are scalable to >10,000 L stainless steel reactors. Culture growth and analysis were performed as described herein (see Example 35).

It is to be understood that the words which have been used are words of description rather than limitation, and that changes may be made within the purview of the appended claims without departing from the true scope and spirit of the invention in its broader aspects.

While the present invention has been described at some length and with some particularity with respect to the several described embodiments, it is not intended that it should be limited to any such particulars or embodiments or any particular embodiment, but it is to be construed with references to the appended claims so as to provide the broadest possible interpretation of such claims in view of the prior art and, therefore, to effectively encompass the intended scope of the invention.

All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, section headings, the materials, methods, and examples are illustrative only and not intended to be limiting.

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acguguacca gaggucguau ugccauccga uugaaacucu uguggauauc uuucaagaau 240

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gaugcugcaa ugaugaaggg uuggagugug uccccacgga ggagucgaau aucacaaugc 360

aaaucaugcg caucaaacca caucaggguc agcauauugg agagaugucc uuucuccagc 420

acaacaaaug ugaguguaga ccgaagaagg accgagcccg acaggaaaac ccaugcggac 480

cgugcuccga gcggcgcaaa cacuuguucg uacaagaccc ccagacaugc aagugcucau 540

guaagaauac cgauucgcgg uguaaggcga gacagcugga auugaacgag cgcacgugua 600

ggugcgacaa gccuagacgg ugagcugccu ucugcggggc uugccuucug gccaugcccu 660

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Cys Cys Leu Val Pro Val Ser Leu Ala
20 25

<210> SEQ ID NO 15
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<400> SEQUENCE: 15

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Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
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Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg
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<210> SEQ ID NO 16
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<212> TYPE: PRT
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<400> SEQUENCE: 16

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1 5 10 15

Gln Ser Val Ala Pro
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<210> SEQ ID NO 17
<211> LENGTH: 24
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

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1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg
20

We claim:

1. A method of producing a polypeptide of interest in a cell in a subject in need thereof, comprising administering to the subject a pharmaceutical composition comprising a modified messenger RNA (mmRNA) such that the mmRNA is introduced into the cell, wherein the mmRNA comprises a translatable region encoding the polypeptide of interest and comprises the modified nucleoside 1-methyl-pseudouridine, and wherein the pharmaceutical composition comprises an effective amount of the mmRNA providing for increased polypeptide production and substantially reduced innate immune response in the cell, as compared to a composition comprising a corresponding unmodified mRNA.

2. A pharmaceutical composition comprising:

a plurality of lipid nanoparticles comprising a cationic lipid, a sterol, and a PEG-lipid,

wherein the lipid nanoparticles comprise an mRNA encoding a polypeptide, wherein the mRNA comprises one or more uridines, one or more cytidines, one or more adenosines, and one or more guanosines and wherein substantially all uridines are modified uridines.

3. The pharmaceutical composition of claim 2, wherein the plurality of lipid nanoparticles further comprise a phosphatidyl choline.

4. The pharmaceutical composition of claim 2, wherein the sterol is cholesterol.

5. The pharmaceutical composition of claim 2, wherein the plurality of lipid nanoparticles has a mean lipid to polynucleotide ratio (wt/wt) of between 10 to 1 and 20 to 1.

6. The pharmaceutical composition of claim 2, wherein the modified uridine is modified on the major groove face of the uridine.

7. The pharmaceutical composition of claim 2, wherein the modified uridine is a pyridine-4-one ribonucleoside, 5-aza-uridine, 2-thio-5-aza-uridine, 2-thio-uridine, 4-thio-pseudouridine, 2-thio-pseudouridine, 5-hydroxy-uridine, 3-methyl-uridine, 5-carboxymethyl-uridine, 1-carboxymethyl-pseudouridine, 5-propynyl-uridine, 1-propynyl-pseudouridine, 5-taurinomethyl-uridine, 1-taurinomethyl-pseudouridine, 5-taurinomethyl-2-thio-uridine, 1-taurino-4-thio-pseudouridine, 1-methyl-pseudouridine, 4-thio-1-methyl-pseudouridine, 2-thio-1-methyl-pseudouridine, 1-methyl-1deaza-pseudouridine, 2-thio-1-methyl-1-deaza-pseudouridine, dihydro-uridine, dihydro-pseudouridine, 2-thio-dihydro-uridine, 2-thio-dihydro-pseudouridine, 2-methoxy-uridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, 4-methoxy-2-thio-pseudouridine, or pseudouridine.

8. The pharmaceutical composition of claim 2, wherein the modified uridine is pseudouridine or 1-methyl-pseudouridine.

9. The pharmaceutical composition of claim 2, wherein the modified uridine is 1-methyl-pseudouridine.

10. The pharmaceutical composition of claim 2, wherein the mRNA further comprises an operably-linked signal sequence.

* * * * *

EXHIBIT 2

US010702600B1

(12) **United States Patent**
Ciaramella et al.

(10) **Patent No.: US 10,702,600 B1**
(45) **Date of Patent: Jul. 7, 2020**

(54) **BETACORONAVIRUS MRNA VACCINE**

(71) Applicant: **ModernaTX, Inc.**, Cambridge, MA (US)

(72) Inventors: **Giuseppe Ciaramella**, Sudbury, MA (US); **Sunny Himansu**, Winchester, MA (US)

(73) Assignee: **ModernaTX, Inc.**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **16/805,587**

(22) Filed: **Feb. 28, 2020**

Related U.S. Application Data

(63) Continuation of application No. 16/368,270, filed on Mar. 28, 2019, which is a continuation of application No. 16/040,981, filed on Jul. 20, 2018, now Pat. No. 10,272,150, which is a continuation of application No. 15/674,599, filed on Aug. 11, 2017, now Pat. No. 10,064,934, which is a continuation of application No. PCT/US2016/058327, filed on Oct. 21, 2016.

(60) Provisional application No. 62/247,362, filed on Oct. 28, 2015, provisional application No. 62/247,394, filed on Oct. 28, 2015, provisional application No. 62/247,483, filed on Oct. 28, 2015, provisional application No. 62/247,297, filed on Oct. 28, 2015, provisional application No. 62/244,802, filed on Oct. 22, 2015, provisional application No. 62/244,946, filed on Oct. 22, 2015, provisional application No. 62/244,813, filed on Oct. 22, 2015, provisional application No. 62/244,837, filed on Oct. 22, 2015, provisional application No. 62/245,031, filed on Oct. 22, 2015.

(51) **Int. Cl.**

A61P 11/00	(2006.01)
A61K 39/12	(2006.01)
A61K 39/215	(2006.01)
A61K 39/155	(2006.01)
C07K 16/10	(2006.01)
A61K 39/00	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 39/155*** (2013.01); ***A61K 39/12*** (2013.01); ***A61K 39/215*** (2013.01); ***A61P 11/00*** (2018.01); ***C07K 16/10*** (2013.01); ***C07K 16/1027*** (2013.01); *A61K 2039/53* (2013.01); *A61K 2039/55511* (2013.01); *A61K 2039/55555* (2013.01); *A61K 2039/6018* (2013.01); *A61K 2039/70* (2013.01); *C07K 2317/76* (2013.01); *C12N 2760/18034* (2013.01); *C12N 2760/18334* (2013.01); *C12N 2760/18434* (2013.01); *C12N 2760/18534* (2013.01); *C12N 2760/18634* (2013.01); *C12N 2770/20034* (2013.01); *Y02A 50/381* (2018.01); *Y02A 50/39* (2018.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

The disclosure relates to respiratory virus ribonucleic acid (RNA) vaccines and combination vaccines, as well as methods of using the vaccines and compositions comprising the vaccines.

26 Claims, 24 Drawing Sheets

Specification includes a Sequence Listing.

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Fig. 1

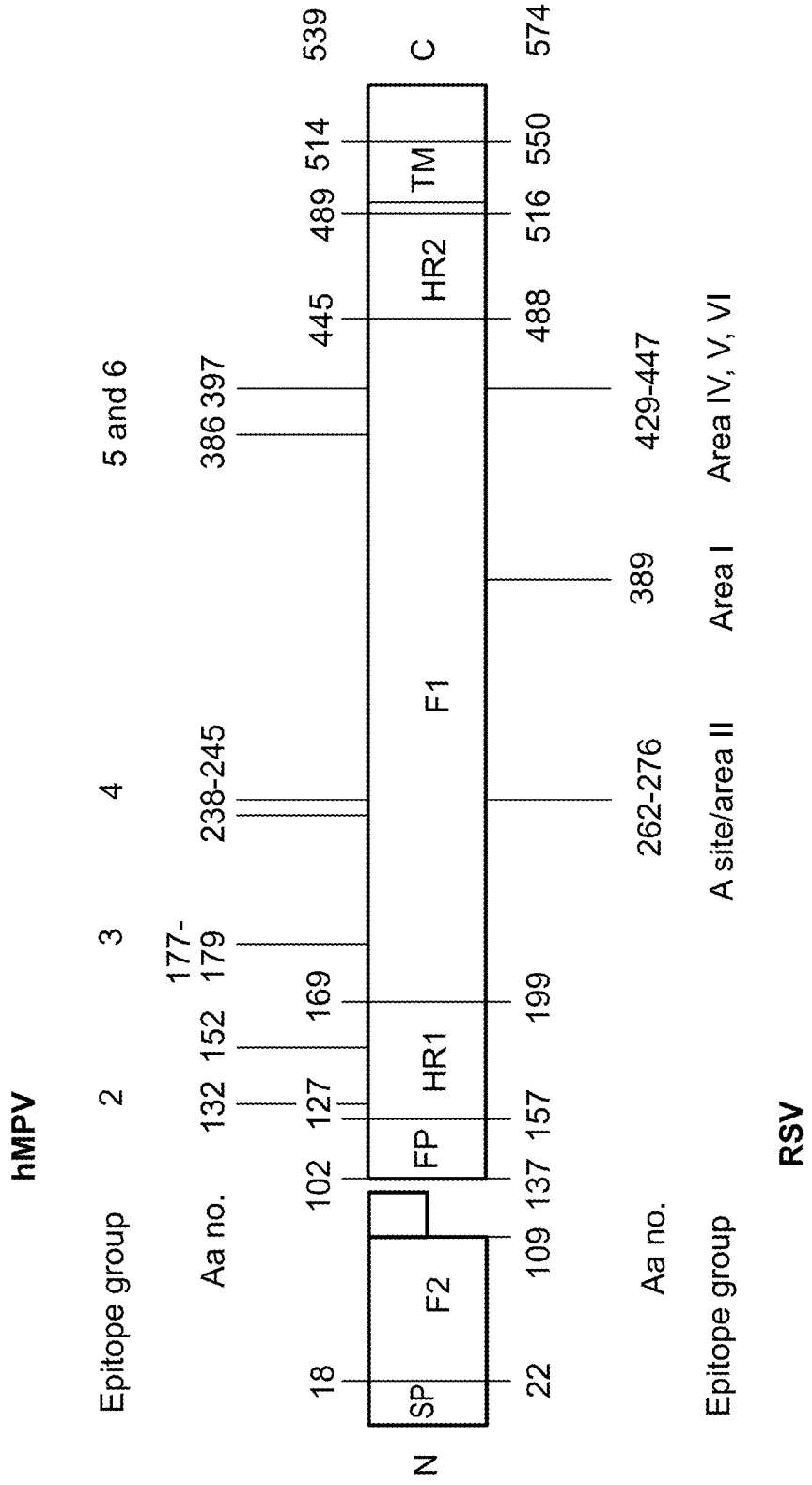
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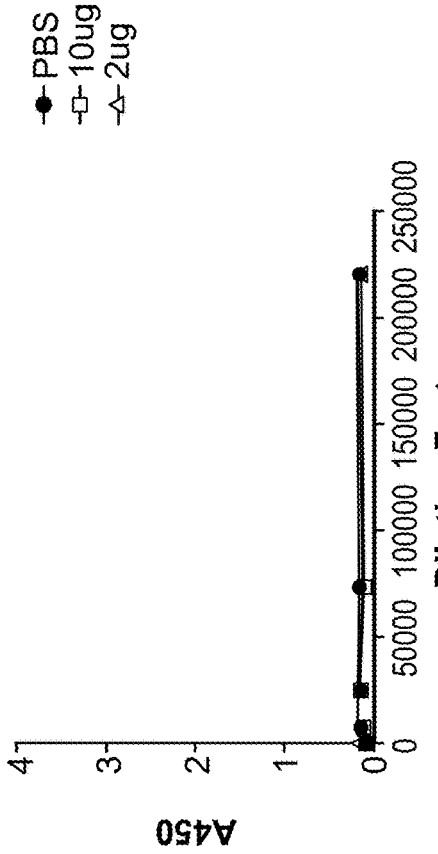
Fig. 2A



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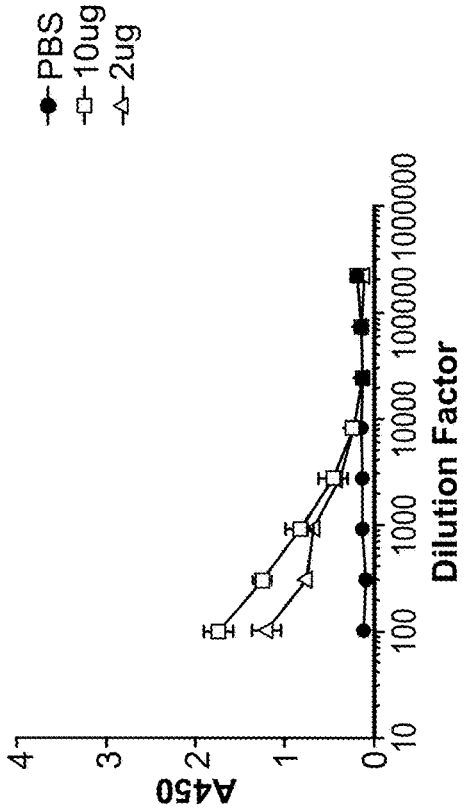

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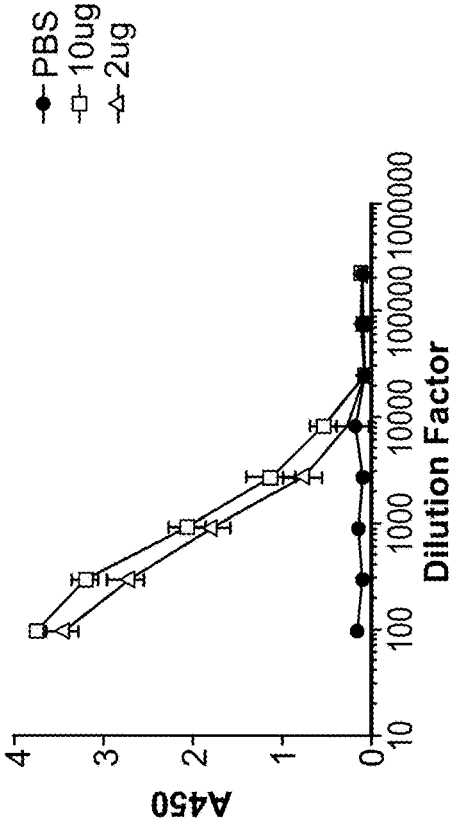


Fig. 3B

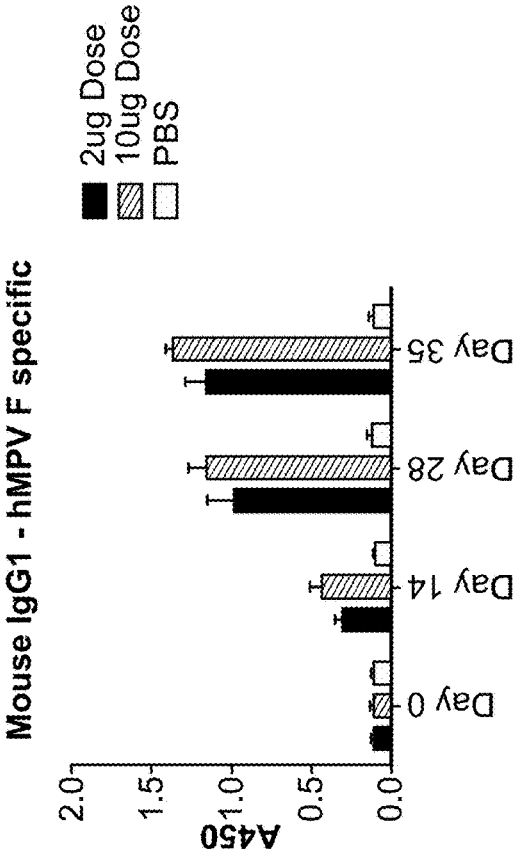


Fig. 3A

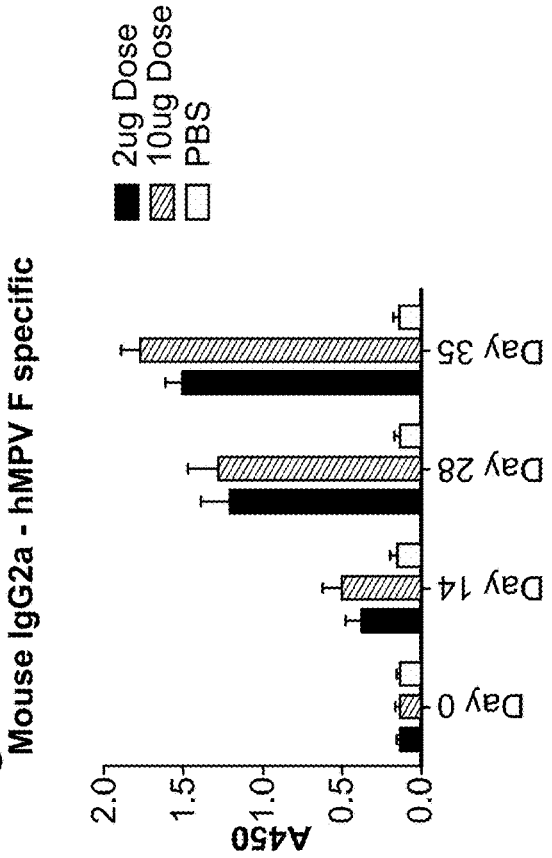


Fig. 3C

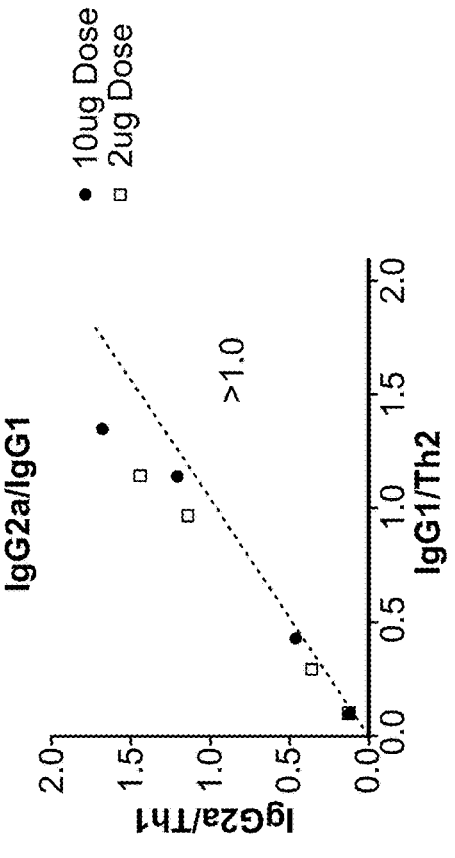
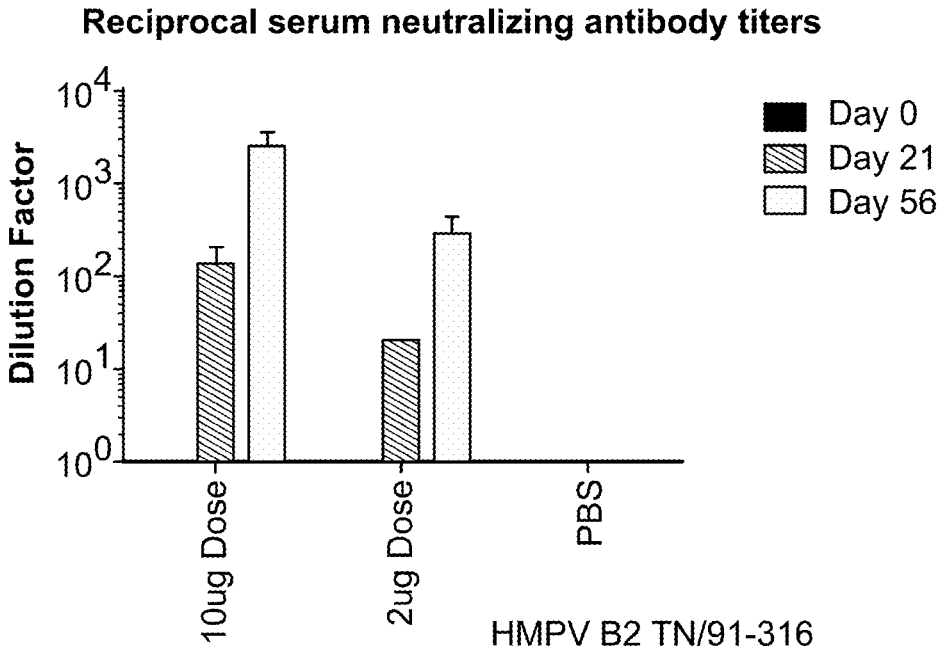


Fig. 4


Reciprocal serum neutralizing antibody titers
Dilution Factor
10^4
10^3
10^2
10^1
10^0
Day 0
Day 21
Day 56
10ug Dose
2ug Dose
PBS
HMPV B2 TN/91-316

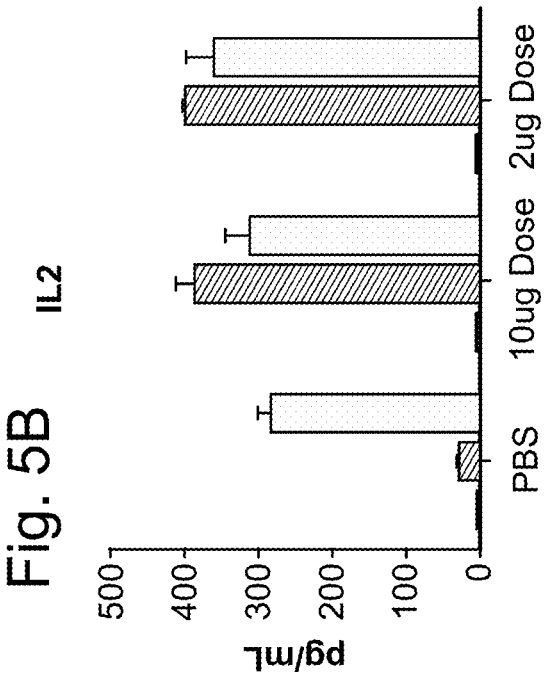
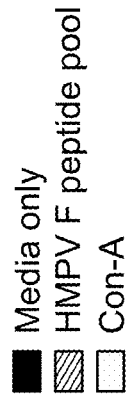


Fig. 5B



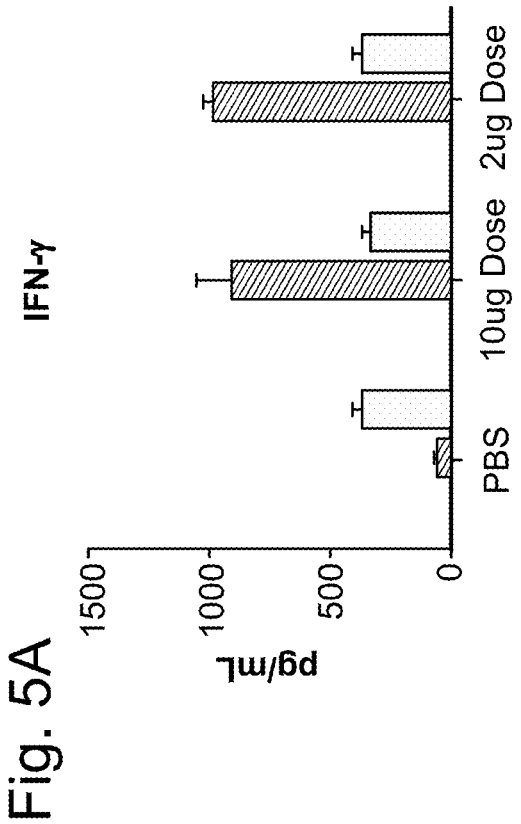


Fig. 5A

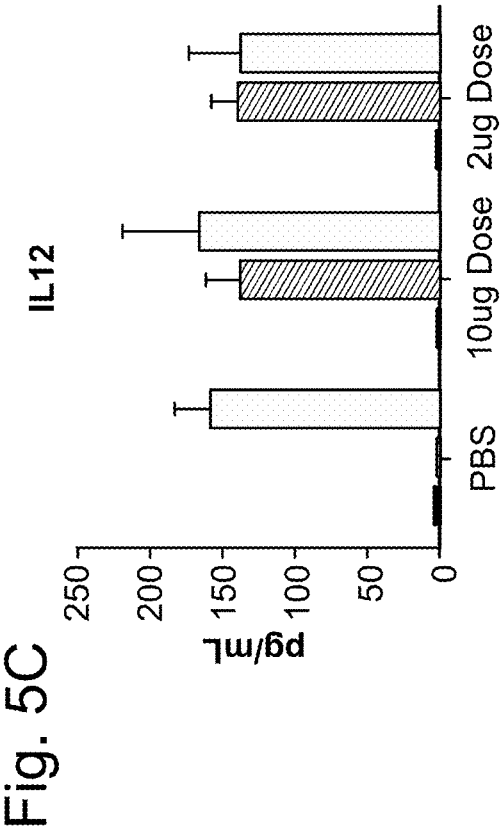
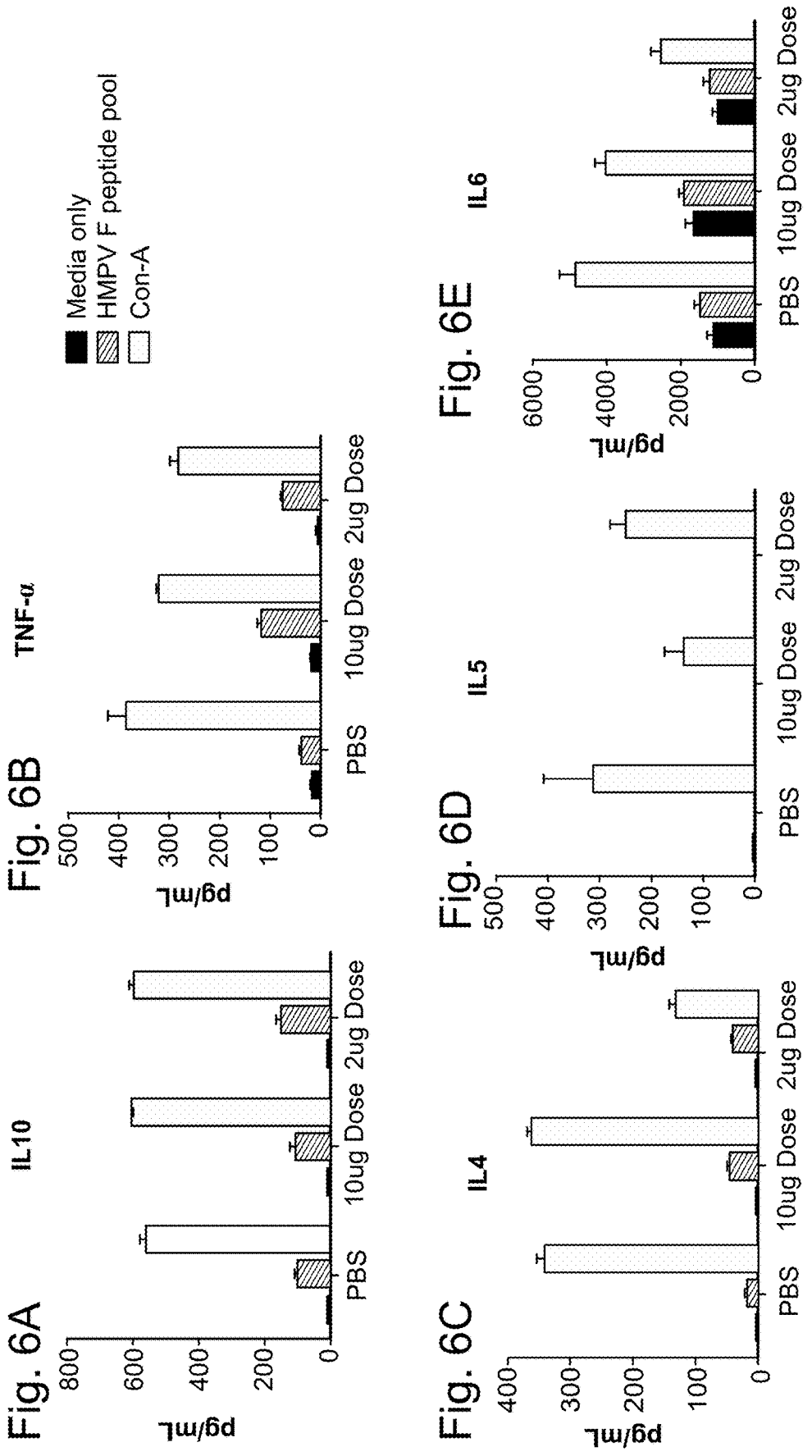


Fig. 5C


Media only
HMPV F peptide pool
Con-A
Fig. 6A
IL10
pg/mL
0
200
400
600
800
PBS
10ug Dose
2ug Dose
Fig. 6B
TNF-α
pg/mL
0
100
200
300
400
500
PBS
10ug Dose
2ug Dose
Fig. 6C
IL4
pg/mL
0
100
200
300
400
PBS
10ug Dose
2ug Dose
Fig. 6D
IL5
pg/mL
0
100
200
300
400
500
PBS
10ug Dose
2ug Dose
Fig. 6E
IL6
pg/mL
0
2000
4000
6000
PBS
10ug Dose
2ug Dose

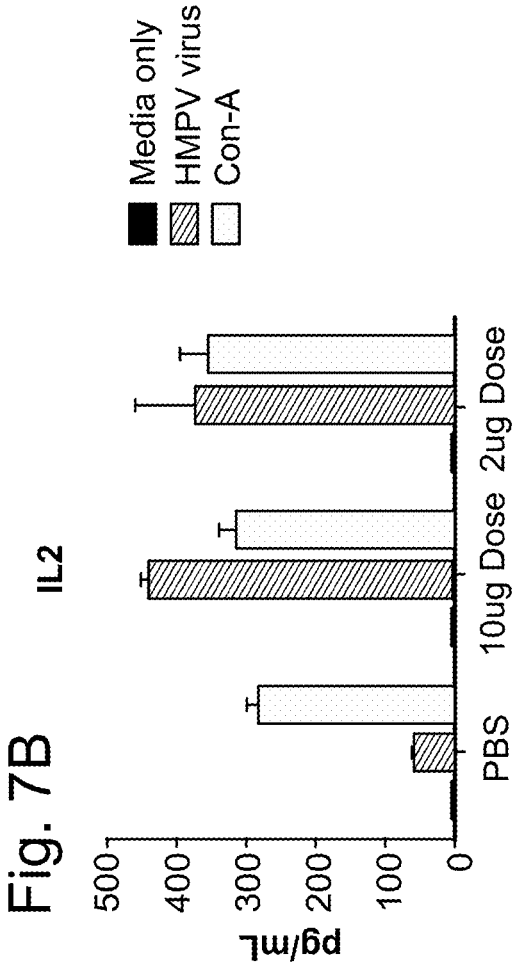


Fig. 7B

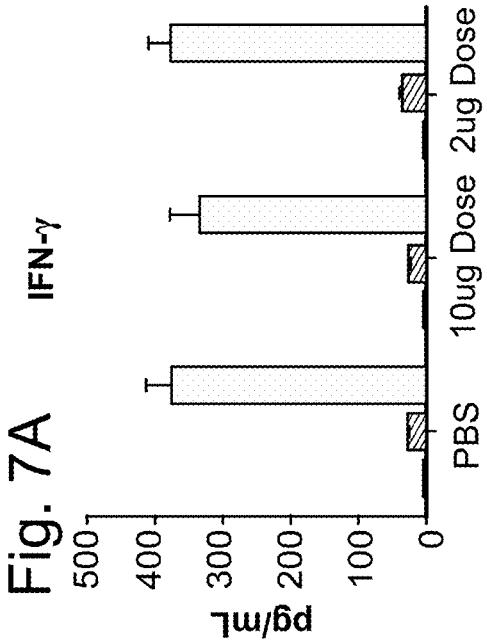


Fig. 7A

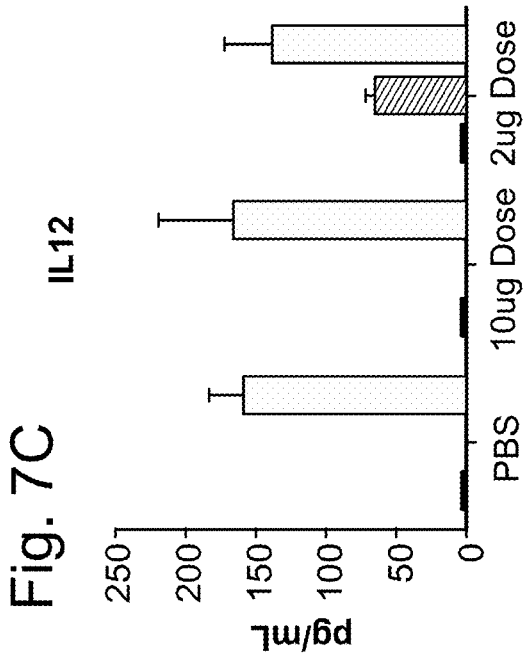


Fig. 7C

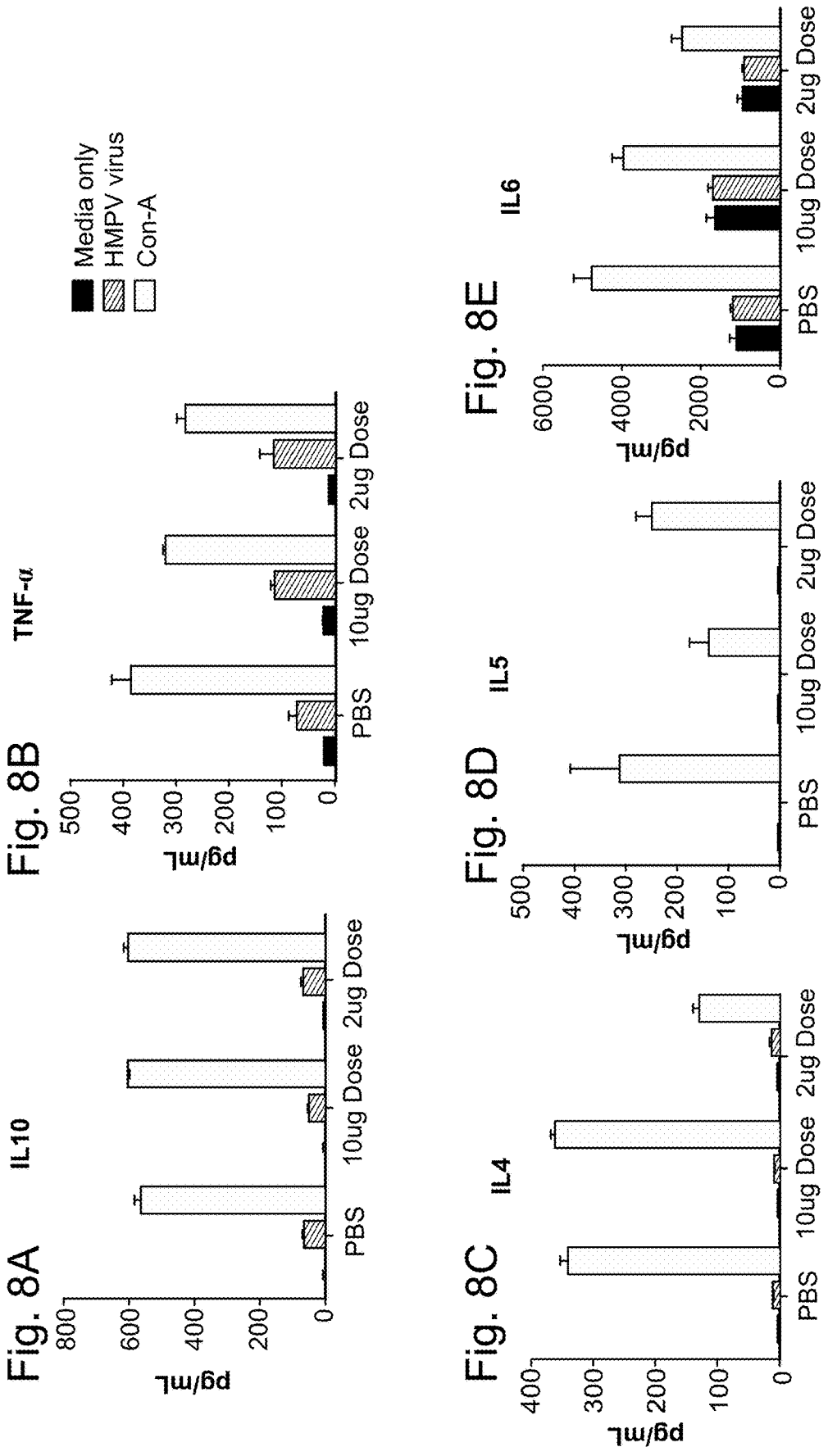

Media only
HMPV virus
Con-A
Fig. 8A
IL10
pg/mL
0
200
400
600
800
PBS
10ug Dose
2ug Dose
Fig. 8B
TNF-α
pg/mL
0
100
200
300
400
500
PBS
10ug Dose
2ug Dose
Fig. 8C
IL4
pg/mL
0
100
200
300
400
PBS
10ug Dose
2ug Dose
Fig. 8D
IL5
pg/mL
0
100
200
300
400
500
PBS
10ug Dose
2ug Dose
Fig. 8E
IL6
pg/mL
0
2000
4000
6000
PBS
10ug Dose
2ug Dose

Fig. 9A

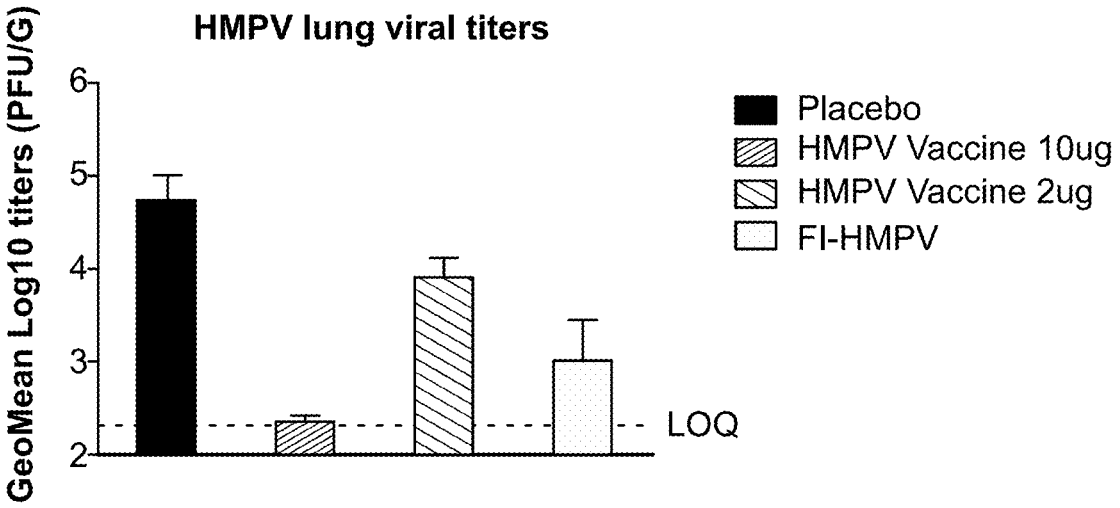

HMPV lung viral titers
GeoMean Log10 titers (PFU/G)
6
5
4
3
2
LOQ
Placebo
HMPV Vaccine 10ug
HMPV Vaccine 2ug
FI-HMPV

Fig. 9B

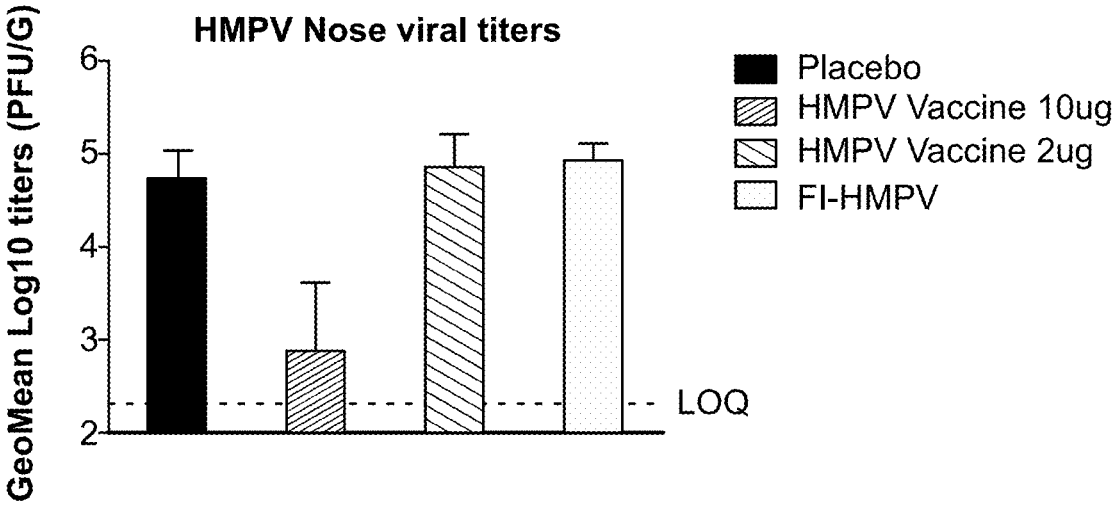

HMPV Nose viral titers
GeoMean Log10 titers (PFU/G)
6
5
4
3
2
LOQ
Placebo
HMPV Vaccine 10ug
HMPV Vaccine 2ug
FI-HMPV

Fig. 10

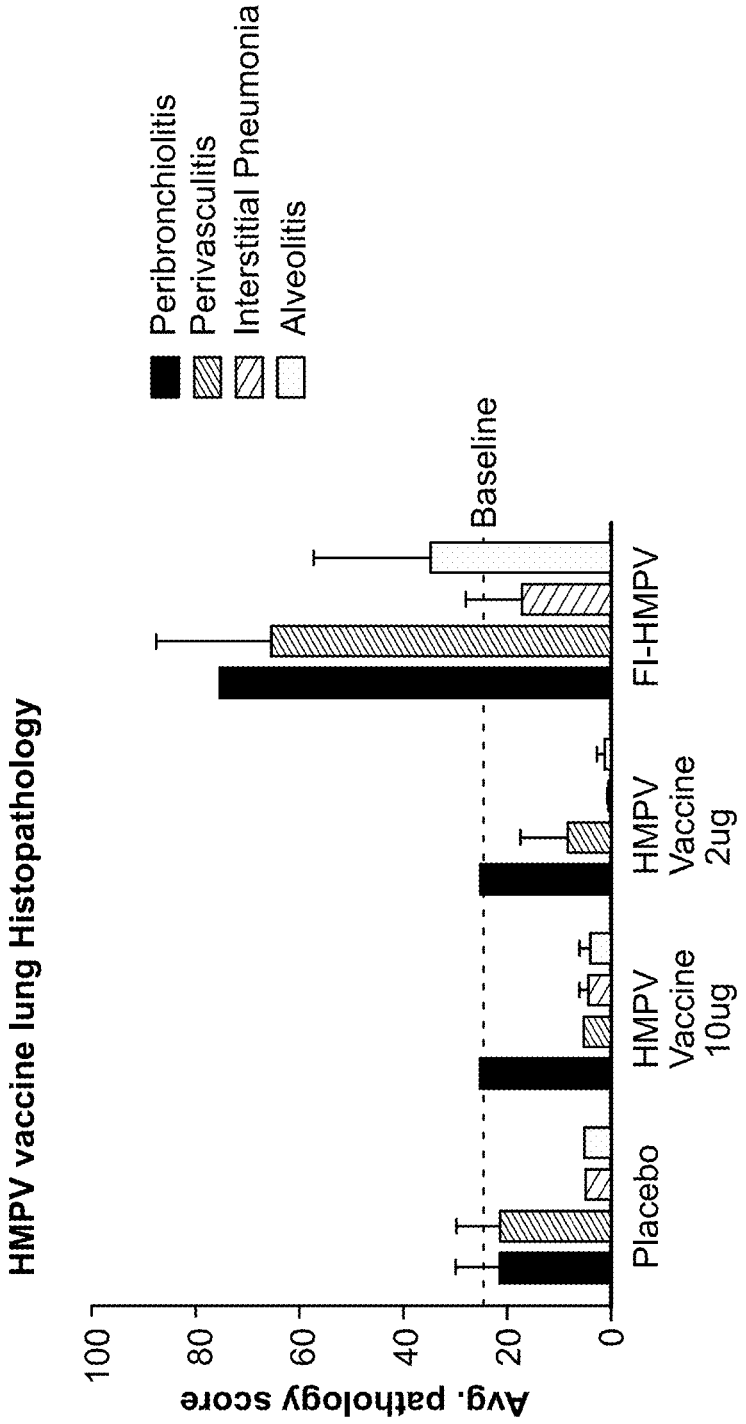
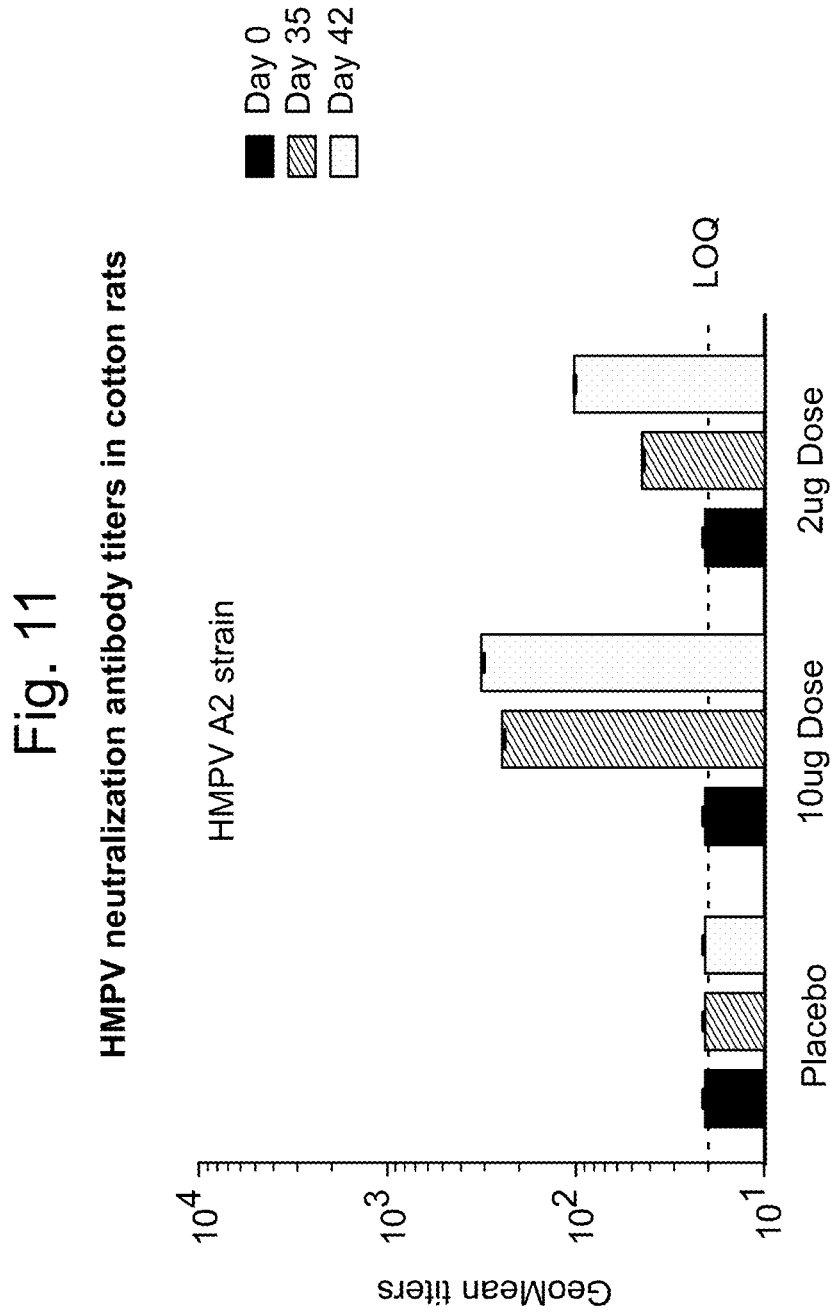

HMPV vaccine lung Histopathology
Peribronchiolitis
Perivasculitis
Interstitial Pneumonia
Alveolitis
Avg. pathology score
100
80
60
40
20
0
Baseline
Placebo
HMPV Vaccine 10ug
HMPV Vaccine 2ug
FI-HMPV

Fig. 11


HMPV neutralization antibody titers in cotton rats
HMPV A2 strain
Day 0
Day 35
Day 42
LOQ
GeoMean titers
10^4
10^3
10^2
10^1
Placebo
10ug Dose
2ug Dose

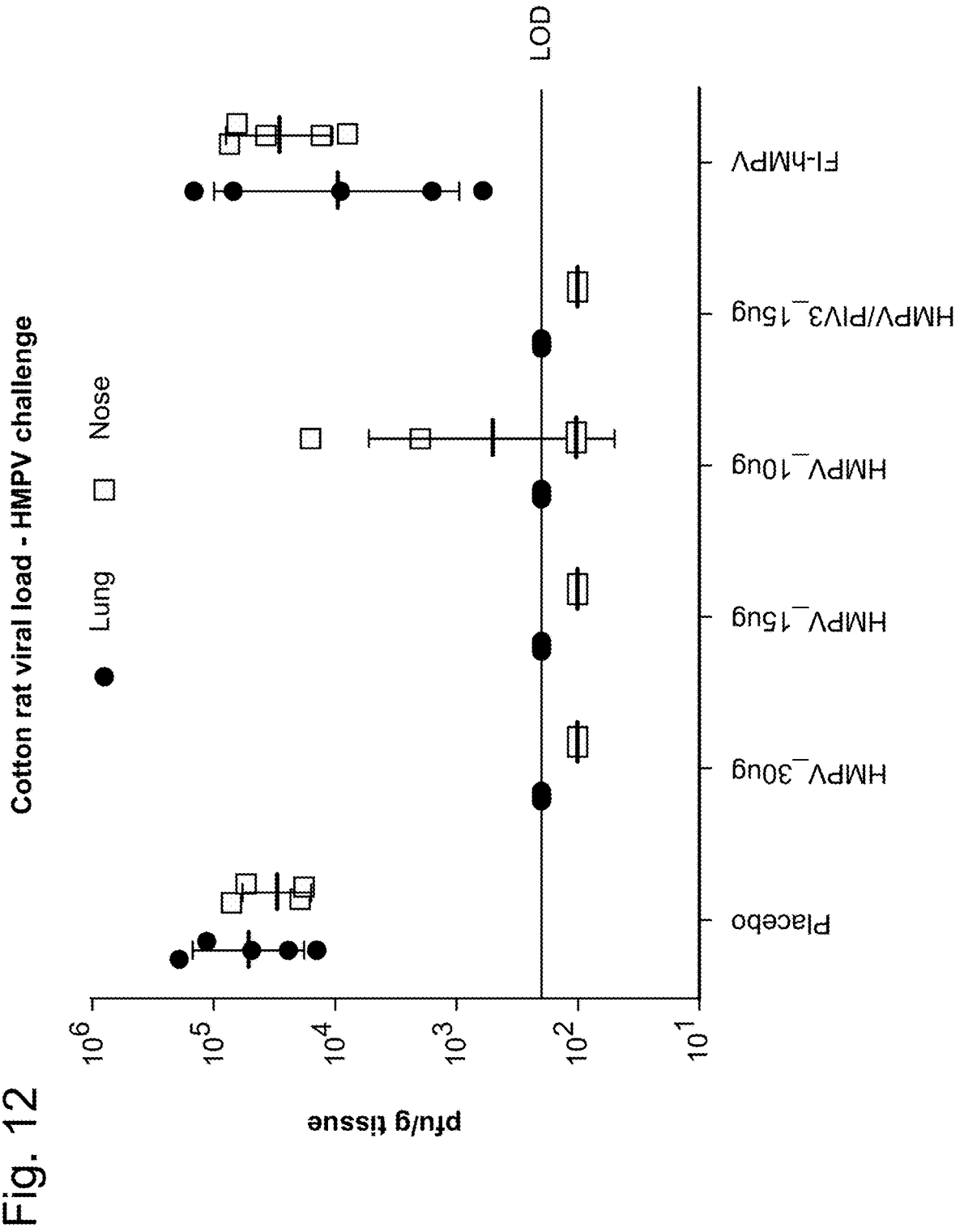

Cotton rat viral load - HMPV challenge
Lung
Nose
LOD
Fl-hMPV
HMPV/PIV3_15ug
HMPV_10ug
HMPV_15ug
HMPV_30ug
Placebo
10^6
10^5
10^4
10^3
10^2
10^1
pfu/g tissue

Fig. 12

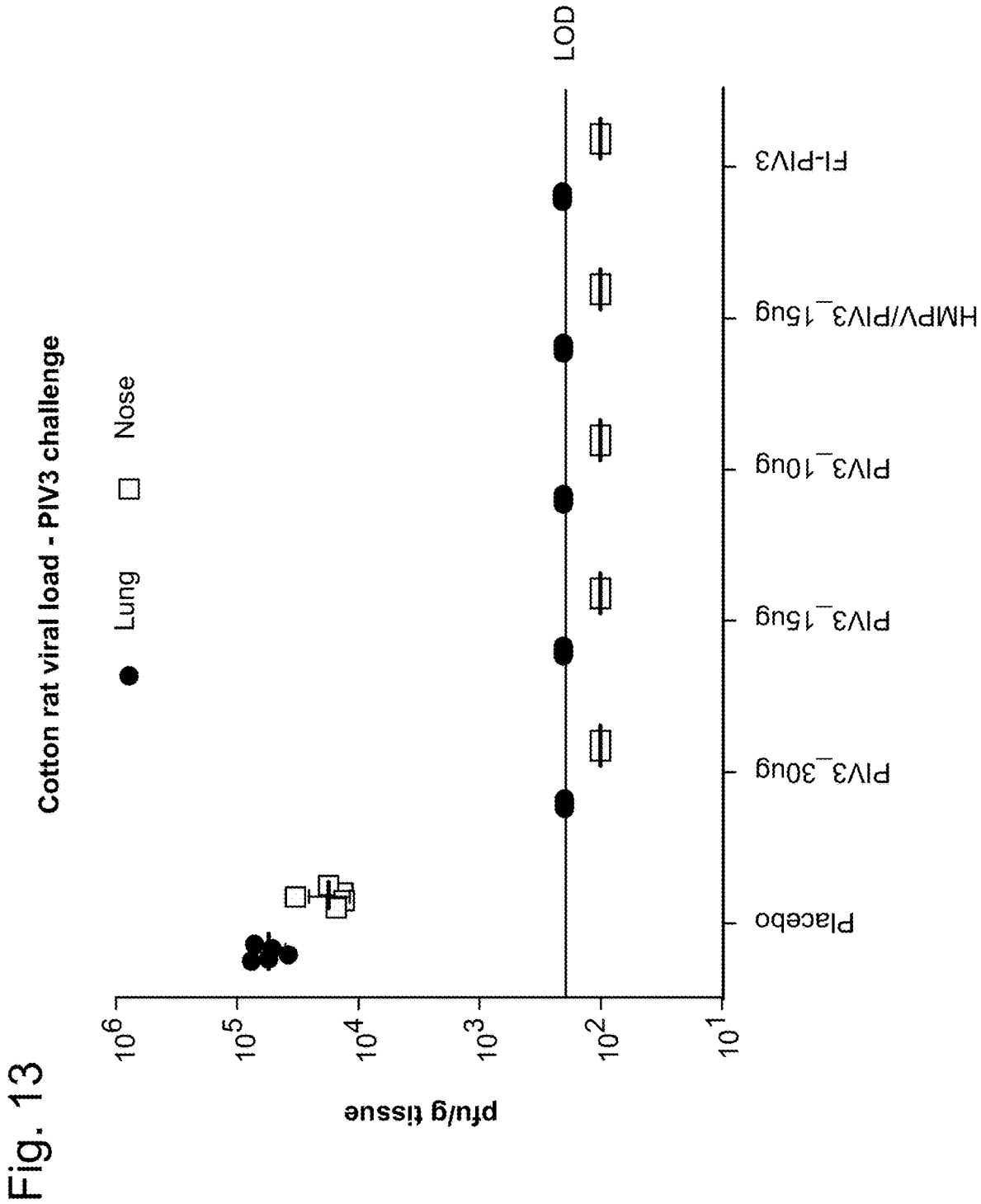

Cotton rat viral load - PIV3 challenge
Lung
Nose
LOD
pfu/g tissue
10^6
10^5
10^4
10^3
10^2
10^1
Placebo
PIV3_30ug
PIV3_15ug
PIV3_10ug
HMPV/PIV3_15ug
FI-PIV3

Fig. 13

Fig. 14

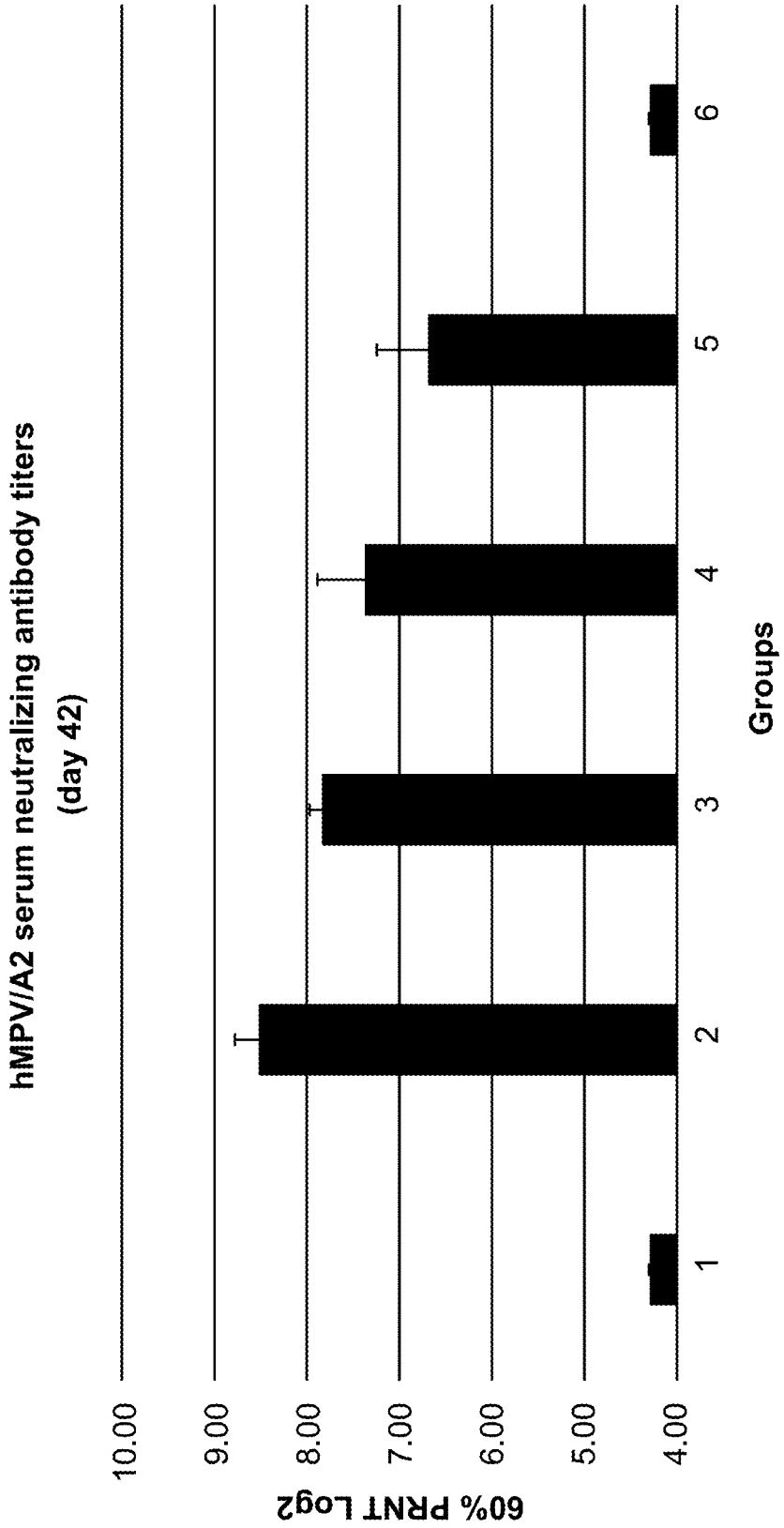

hMPV/A2 serum neutralizing antibody titers
(day 42)
60% PRNT Log2
10.00
9.00
8.00
7.00
6.00
5.00
4.00
1
2
3
4
5
6
Groups

Fig. 15

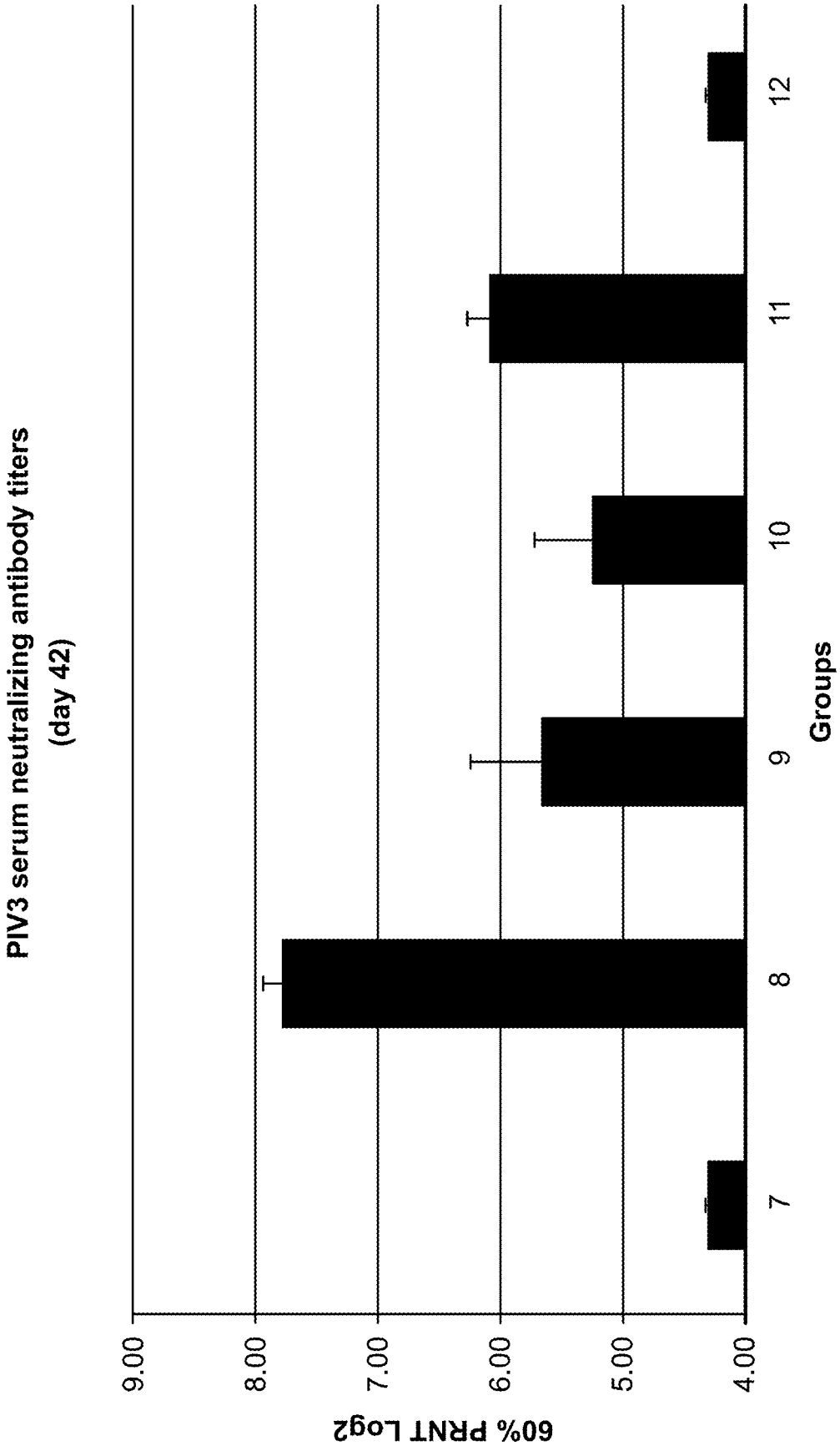

PIV3 serum neutralizing antibody titers
(day 42)
60% PRNT Log2
9.00
8.00
7.00
6.00
5.00
4.00
7
8
9
10
11
12
Groups

Fig. 16

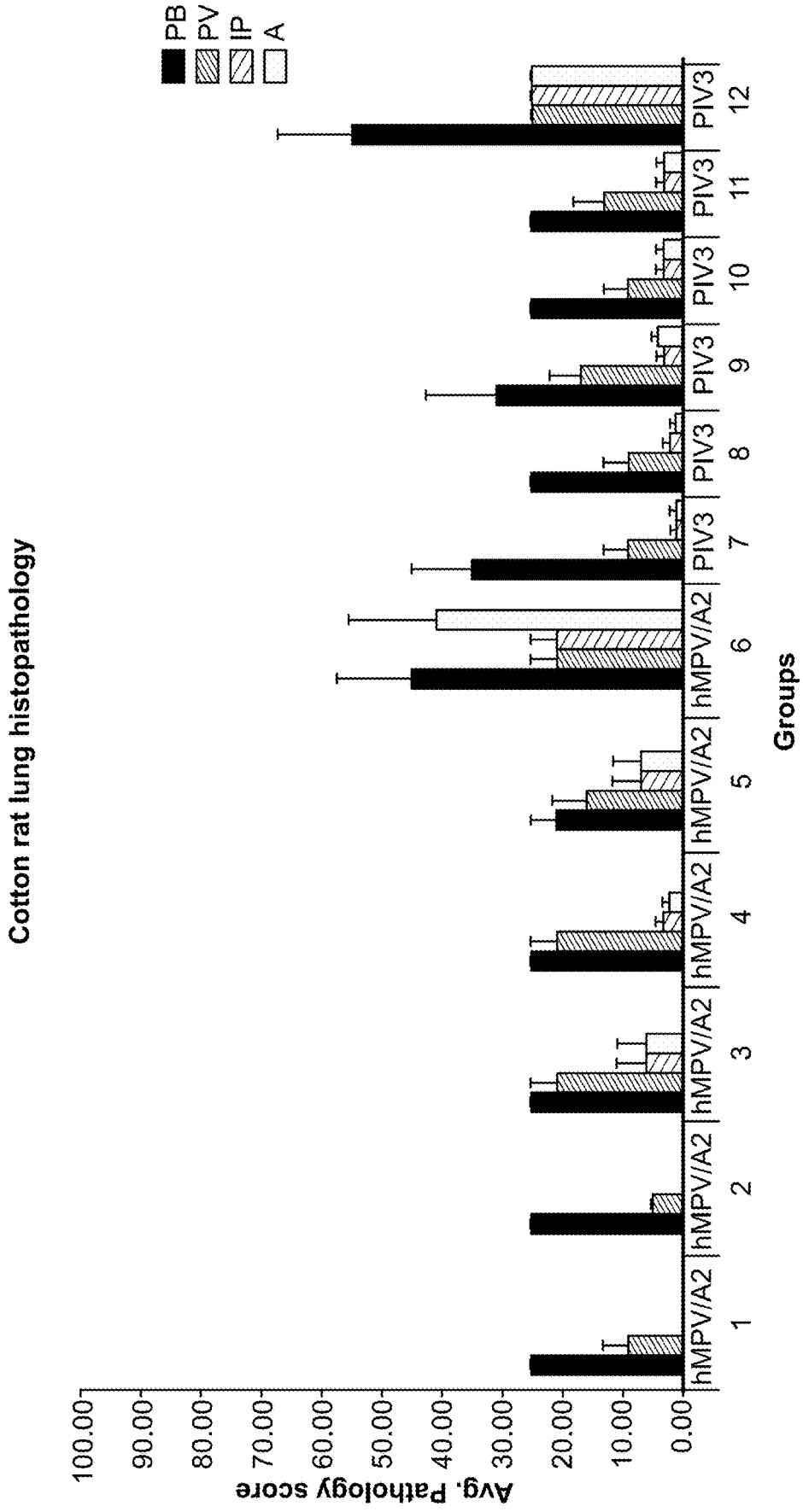

Cotton rat lung histopathology
PB
PV
IP
A
Avg. Pathology score
100.00
90.00
80.00
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
hMPV/A2
hMPV/A2
hMPV/A2
hMPV/A2
hMPV/A2
hMPV/A2
PIV3
PIV3
PIV3
PIV3
PIV3
PIV3
1
2
3
4
5
6
7
8
9
10
11
12
Groups

Fig. 17

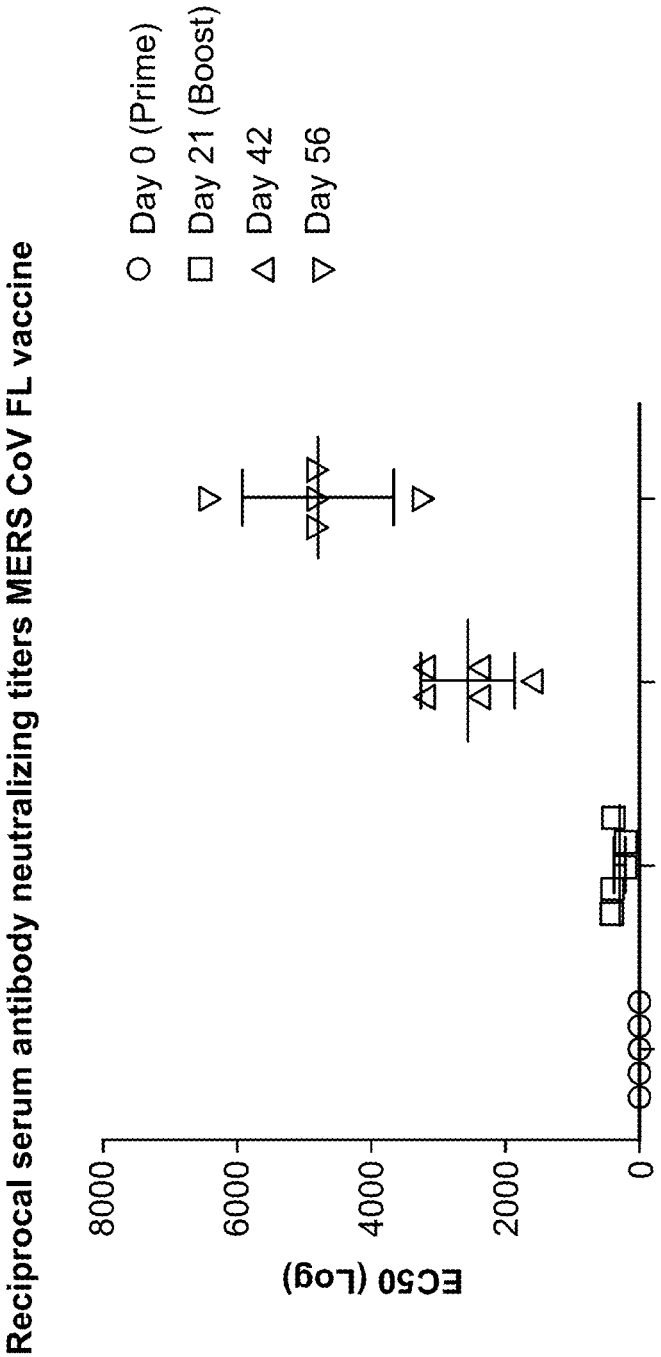

Reciprocal serum antibody neutralizing titers MERS CoV FL vaccine
EC50 (Log)
8000
6000
4000
2000
0
Day 0 (Prime)
Day 21 (Boost)
Day 42
Day 56

Fig. 18

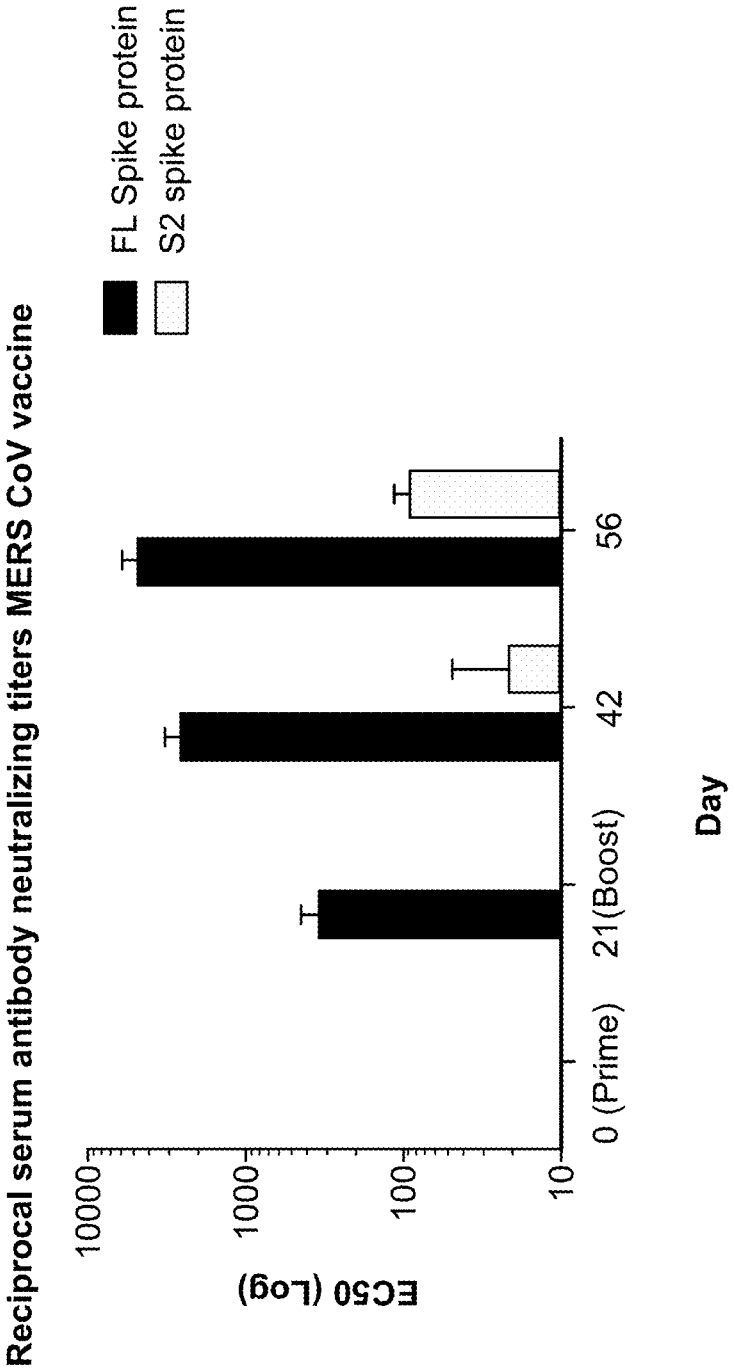

Reciprocal serum antibody neutralizing titers MERS CoV vaccine
FL Spike protein
S2 spike protein
EC50 (Log)
10000
1000
100
10
0 (Prime)
21(Boost)
42
56
Day

Fig. 19A

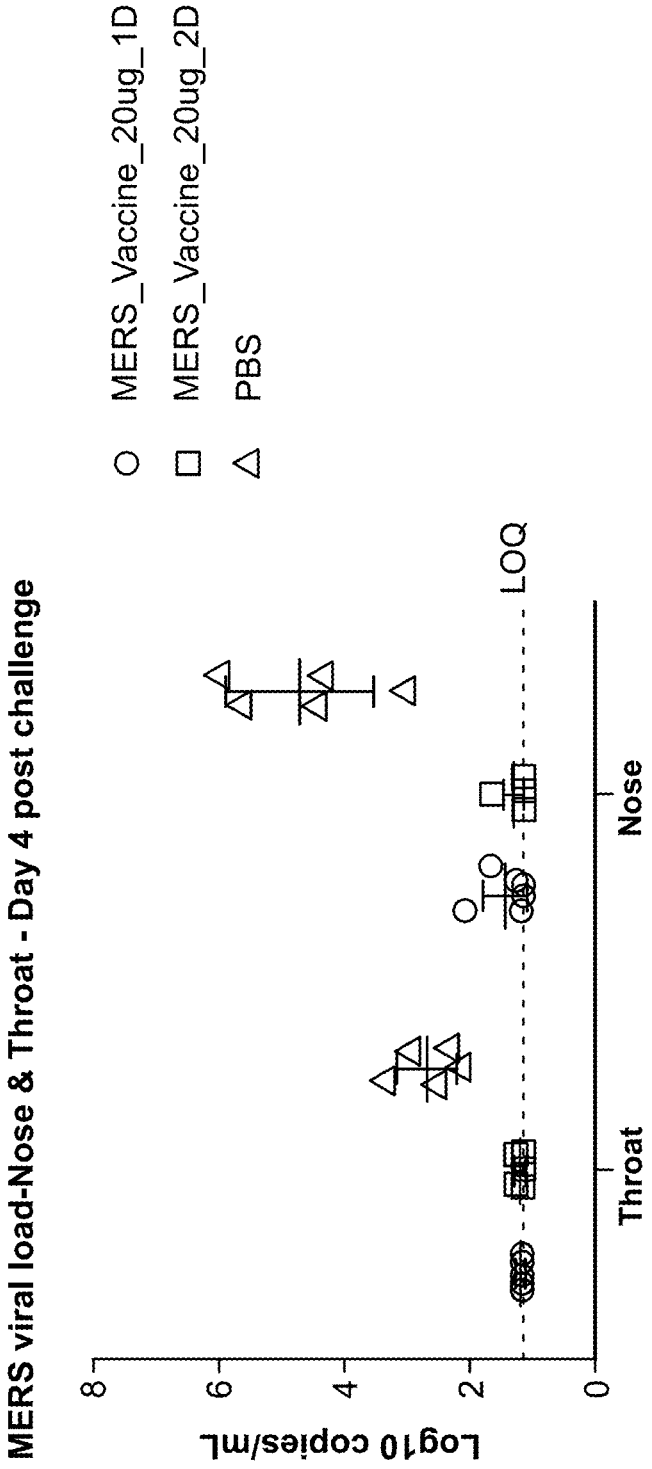

MERS viral load-Nose & Throat - Day 4 post challenge
MERS_Vaccine_20ug_1D
MERS_Vaccine_20ug_2D
PBS
Log10 copies/mL
8
6
4
2
0
LOQ
Nose
Throat

Fig. 19B

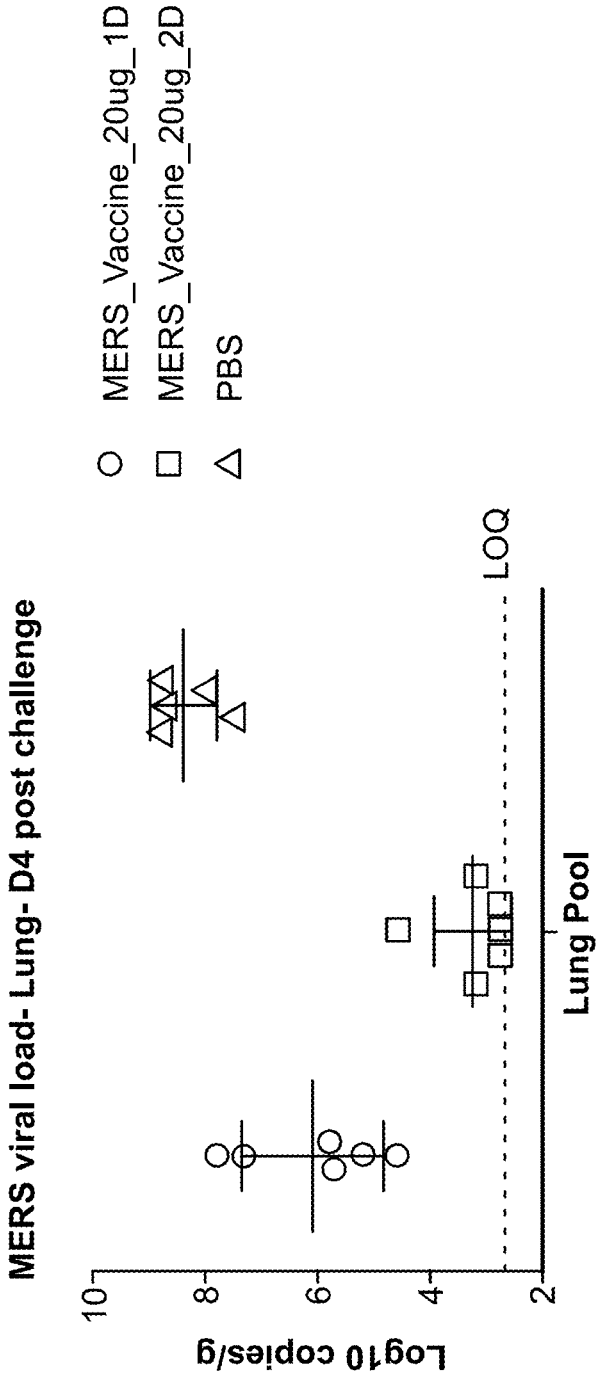

MERS viral load- Lung- D4 post challenge
MERS_Vaccine_20ug_1D
MERS_Vaccine_20ug_2D
PBS
LOQ
Log10 copies/g
10
8
6
4
2
Lung Pool

Fig. 19C

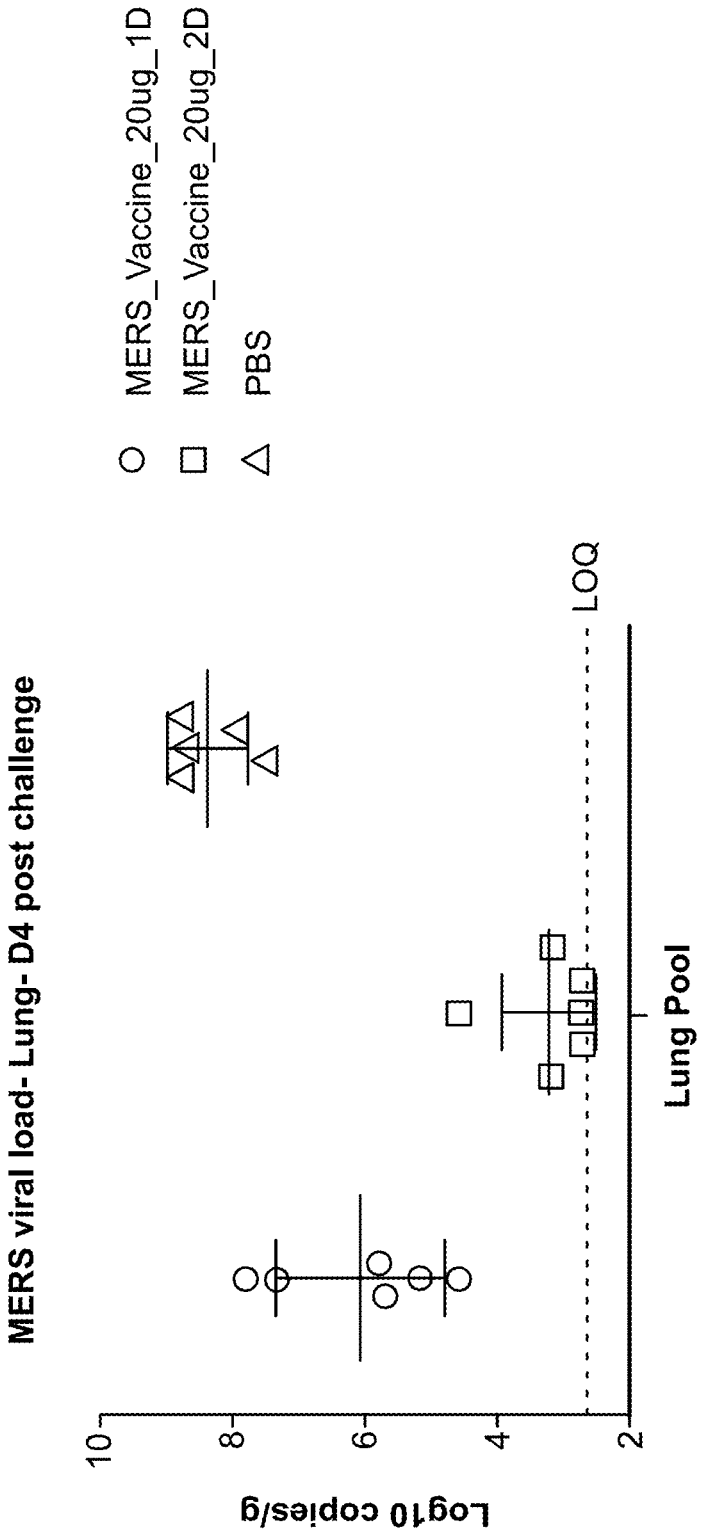

MERS_Vaccine_20ug_1D
MERS_Vaccine_20ug_2D
PBS
MERS viral load- Lung- D4 post challenge
Log10 copies/g
10
8
6
4
2
LOQ
Lung Pool

Fig. 20A

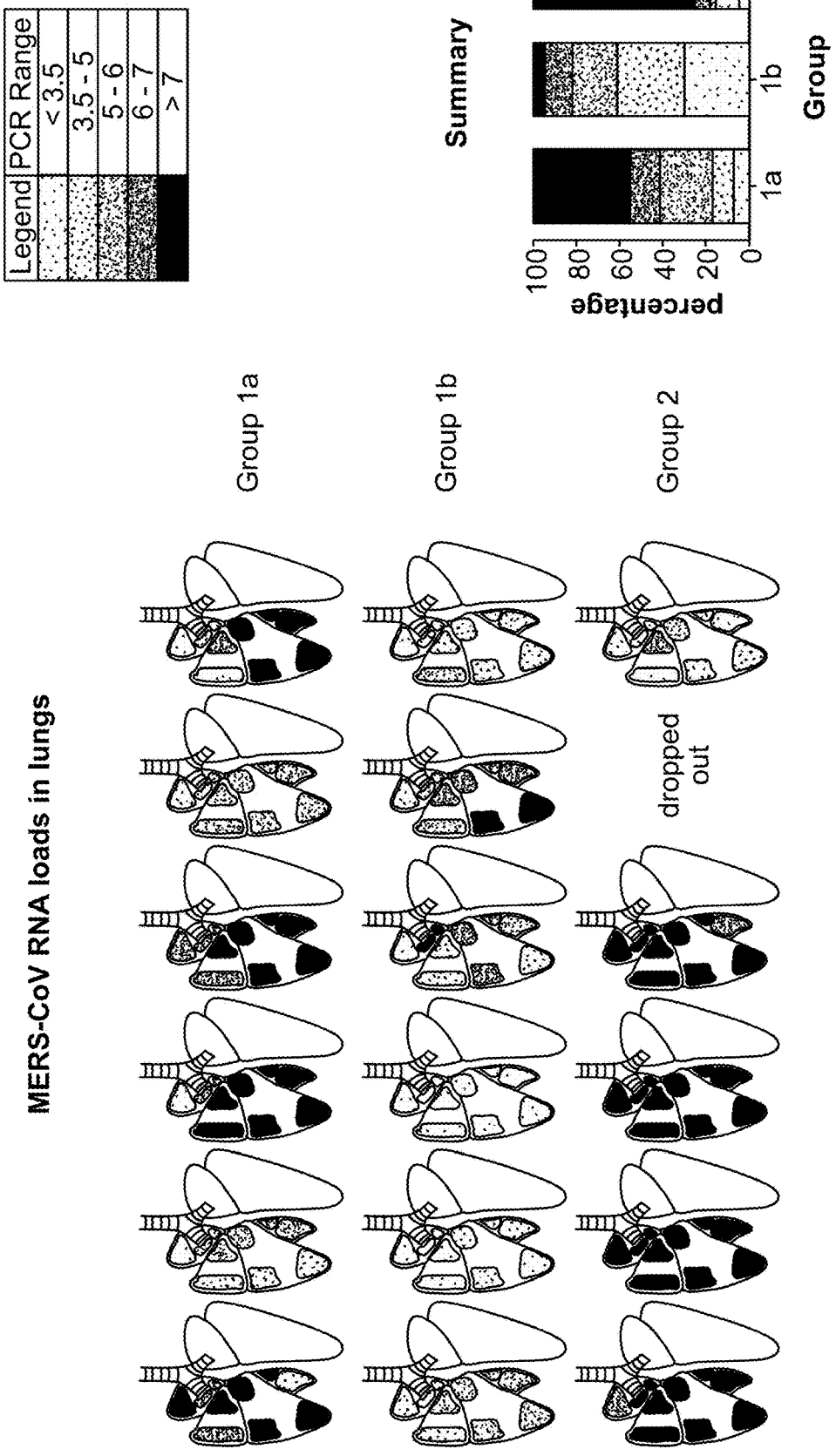

MERS-CoV RNA loads in lungs
Group 1a
Group 1b
Group 2
dropped out
Legend
PCR Range
< 3.5
3.5 - 5
5 - 6
6 - 7
> 7
Summary
percentage
100
80
60
40
20
0
1a
1b
2
Group

Fig. 20B

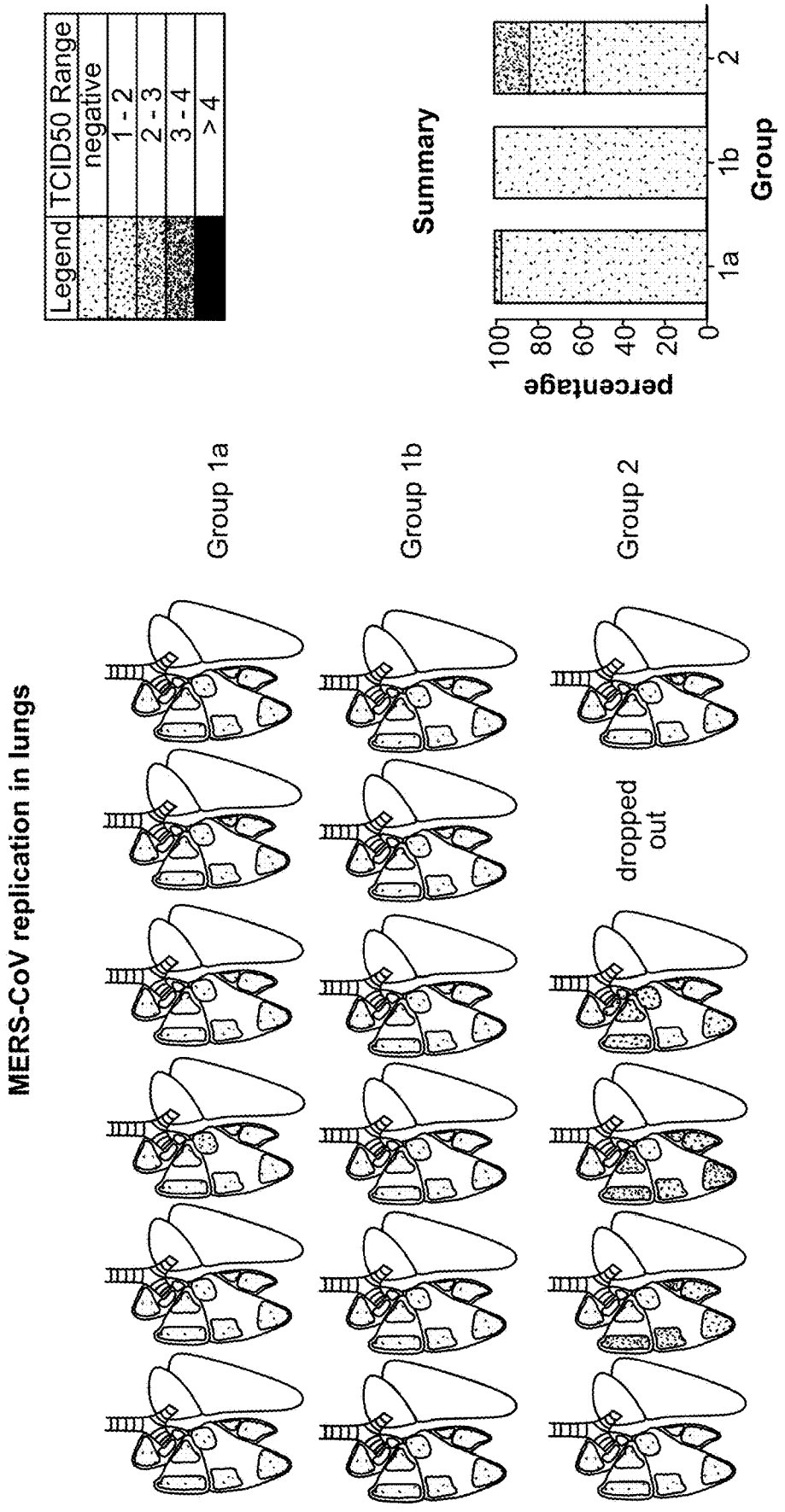
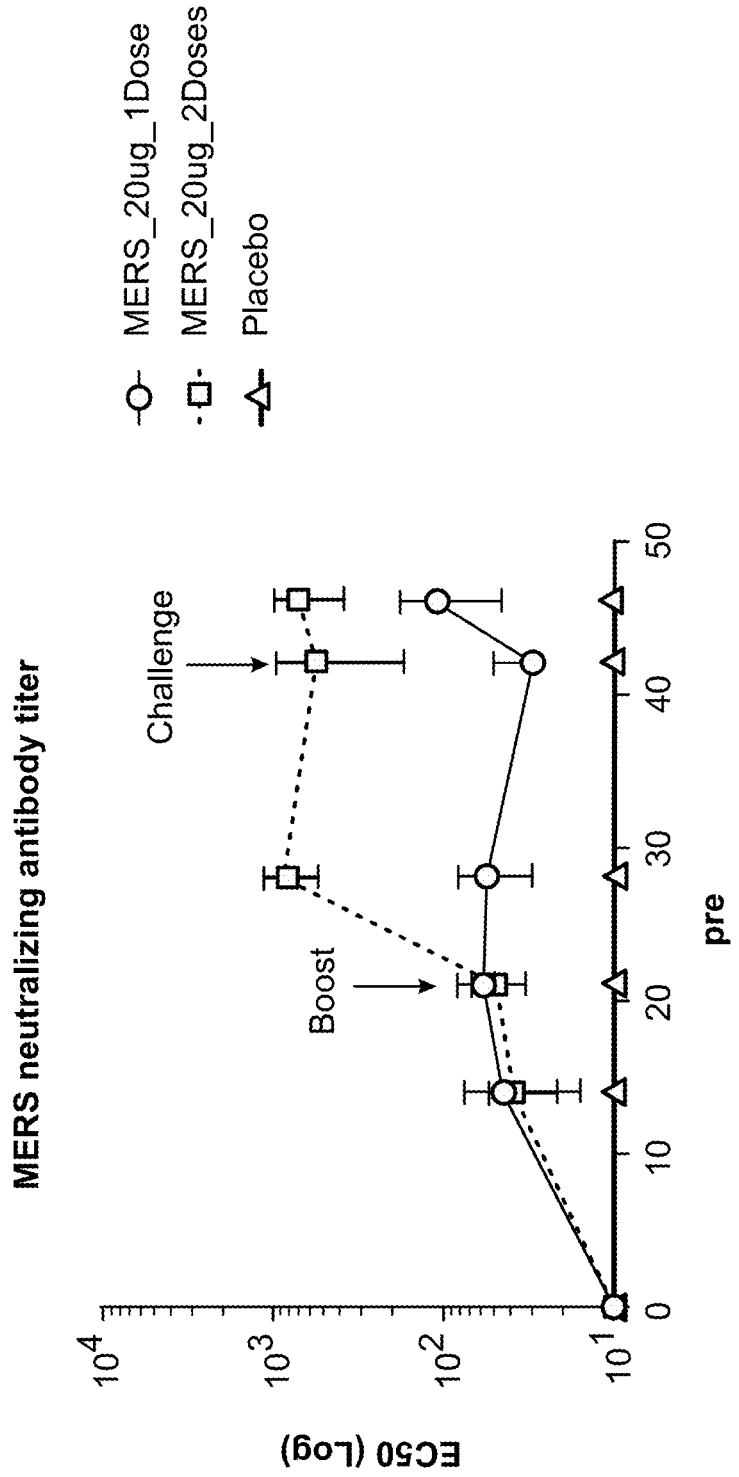

MERS-CoV replication in lungs
Group 1a
Group 1b
Group 2
dropped out
Legend
TCID50 Range
negative
1 - 2
2 - 3
3 - 4
> 4
Summary
percentage
100
80
60
40
20
0
1a
1b
2
Group

Fig. 21


MERS_20ug_1Dose
MERS_20ug_2Doses
Placebo
MERS neutralizing antibody titer
Challenge
Boost
pre
0
10
20
30
40
50
10^1
10^2
10^3
10^4
EC50 (Log)

BETACORONAVIRUS MRNA VACCINE

RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 16/368,270, filed Mar. 28, 2019, which is a continuation of Ser. No. 16/040,981, filed Jul. 20, 2018, now U.S. Pat. No. 10,272,150, which is a continuation of U.S. application Ser. No. 15/674,599, filed Aug. 11, 2017, now U.S. Pat. No. 10,064,934, which is a continuation of International application number PCT/US2016/058327, filed Oct. 21, 2016, which claims the benefit under 35 U.S.C. § 119(e) of U.S. provisional application No. 62/244,802, filed Oct. 22, 2015, U.S. provisional application No. 62/247,297, filed Oct. 28, 2015, U.S. provisional application No. 62/244,946, filed Oct. 22, 2015, U.S. provisional application No. 62/247,362, filed Oct. 28, 2015, U.S. provisional application No. 62/244,813, filed Oct. 22, 2015, U.S. provisional application No. 62/247,394, filed Oct. 28, 2015, U.S. provisional application No. 62/244,837, filed Oct. 22, 2015, U.S. provisional application No. 62/247,483, filed Oct. 28, 2015, and U.S. provisional application No. 62/245,031, filed Oct. 22, 2015, each of which is incorporated by reference herein in its entirety.

BACKGROUND

Respiratory disease is a medical term that encompasses pathological conditions affecting the organs and tissues that make gas exchange possible in higher organisms, and includes conditions of the upper respiratory tract, trachea, bronchi, bronchioles, alveoli, pleura and pleural cavity, and the nerves and muscles of breathing. Respiratory diseases range from mild and self-limiting, such as the common cold, to life-threatening entities like bacterial pneumonia, pulmonary embolism, acute asthma and lung cancer. Respiratory disease is a common and significant cause of illness and death around the world. In the US, approximately 1 billion "common colds" occur each year. Respiratory conditions are among the most frequent reasons for hospital stays among children.

The human metapneumovirus (hMPV) is a negative-sense, single-stranded RNA virus of the genus Pneumovirinae and of the family Paramyxoviridae and is closely related to the avian metapneumovirus (AMPV) subgroup C. It was isolated for the first time in 2001 in the Netherlands by using the RAP-PCR (RNA arbitrarily primed PCR) technique for identification of unknown viruses growing in cultured cells. hPMV is second only to RSV as an important cause of viral lower respiratory tract illness (LRI) in young children. The seasonal epidemiology of hMPV appears to be similar to that of RSV, but the incidence of infection and illness appears to be substantially lower.

Parainfluenza virus type 3 (PIV3), like hMPV, is also a negative-sense, single-stranded sense RNA virus of the genus Pneumovirinae and of the family Paramyxoviridae and is a major cause of ubiquitous acute respiratory infections of infancy and early childhood. Its incidence peaks around 4-12 months of age, and the virus is responsible for 3-10% of hospitalizations, mainly for bronchiolitis and pneumonia. PIV3 can be fatal, and in some instances is associated with neurologic diseases, such as febrile seizures. It can also result in airway remodeling, a significant cause of morbidity. In developing regions of the world, infants and young children are at the highest risk of mortality, either from primary PIV3 viral infection or a secondary consequences, such as bacterial infections. Human parainfluenza viruses (hPIV) types 1, 2 and 3 (hPIV1, hPIV2 and hPIV3, respectively), also like hMPV, are second only to RSV as important causes of viral LRI in young children.

RSV, too, is a negative-sense, single-stranded RNA virus of the genus Pneumovirinae and of the family Paramyxoviridae. Symptoms in adults typically resemble a sinus infection or the common cold, although the infection may be asymptomatic. In older adults (e.g., >60 years), RSV infection may progress to bronchiolitis or pneumonia. Symptoms in children are often more severe, including bronchiolitis and pneumonia. It is estimated that in the United States, most children are infected with RSV by the age of three. The RSV virion consists of an internal nucleocapsid comprised of the viral RNA bound to nucleoprotein (N), phosphoprotein (P), and large polymerase protein (L). The nucleocapsid is surrounded by matrix protein (M) and is encapsulated by a lipid bilayer into which the viral fusion (F) and attachment (G) proteins as well as the small hydrophobic protein (SH) are incorporated. The viral genome also encodes two non-structural proteins (NS1 and NS2), which inhibit type I interferon activity as well as the M-2 protein.

The continuing health problems associated with hMPV, PIV3 and RSV are of concern internationally, reinforcing the importance of developing effective and safe vaccine candidates against these virus.

Despite decades of research, no vaccines currently exist (Sato and Wright, *Pediatr. Infect. Dis. J.* 2008; 27(10 Suppl): S123-5). Recombinant technology, however, has been used to target the formation of vaccines for hPIV-1, 2 and 3 serotypes, for example, and has taken the form of several live-attenuated intranasal vaccines. Two vaccines in particular were found to be immunogenic and well tolerated against hPIV-3 in phase I trials. hPIV1 and hPIV2 vaccine candidates remain less advanced (Durbin and Karron, Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 2003; 37(12):1668-77).

Measles virus (MeV), like hMPV, PIV3 and RSV, is a negative-sense, single-stranded RNA virus that is the cause of measles, an infection of the respiratory system. MeV is of the genus Morbillivirus within the family Paramyxoviridae. Humans are the natural hosts of the virus; no animal reservoirs are known to exist. Symptoms of measles include fever, cough, runny nose, red eyes and a generalized, maculopapular, erythematous rash. The virus is highly contagious and is spread by coughing

In additional to hMPV, PIV, RSV and MeV, betacoronaviruses are known to cause respiratory illnesses. Betacoronaviruses (BetaCoVs) are one of four genera of coronaviruses of the subfamily Coronavirinae in the family Coronaviridae, of the order Nidovirales. They are enveloped, positive-sense, single-stranded RNA viruses of zoonotic origin. The coronavirus genera are each composed of varying viral lineages, with the betacoronavirus genus containing four such lineages. The BetaCoVs of the greatest clinical importance concerning humans are OC43 and HKU1 of the A lineage, SARS-CoV of the B lineage, and MERS-CoV of the C lineage. MERS-CoV is the first betacoronavirus belonging to lineage C that is known to infect humans.

The Middle East respiratory syndrome coronavirus (MERS-CoV), or EMC/2012 (HCoV-EMC/2012), initially referred to as novel coronavirus 2012 or simply novel coronavirus, was first reported in 2012 after genome sequencing of a virus isolated from sputum samples from a person who fell ill during a 2012 outbreak of a new flu. As of July 2015, MERS-CoV cases have been reported in over 21 countries. The outbreaks of MERS-CoV have raised

serious concerns world-wide, reinforcing the importance of developing effective and safe vaccine candidates against MERS-CoV.

Severe acute respiratory syndrome (SARS) emerged in China in 2002 and spread to other countries before brought under control. Because of a concern for reemergence or a deliberate release of the SARS coronavirus, vaccine development was initiated.

Deoxyribonucleic acid (DNA) vaccination is one technique used to stimulate humoral and cellular immune responses to foreign antigens, such as hMPV antigens and/or PIV antigens and/or RSV antigens. The direct injection of genetically engineered DNA (e.g., naked plasmid DNA) into a living host results in a small number of its cells directly producing an antigen, resulting in a protective immunological response. With this technique, however, comes potential problems, including the possibility of insertional mutagenesis, which could lead to the activation of oncogenes or the inhibition of tumor suppressor genes.

SUMMARY

Provided herein are ribonucleic acid (RNA) vaccines that build on the knowledge that RNA (e.g., messenger RNA (mRNA)) can safely direct the body's cellular machinery to produce nearly any protein of interest, from native proteins to antibodies and other entirely novel protein constructs that can have therapeutic activity inside and outside of cells. The RNA (e.g., mRNA) vaccines of the present disclosure may be used to induce a balanced immune response against hMPV, PIV, RSV, MeV, and/or BetaCoV (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1), or any combination of two or more of the foregoing viruses, comprising both cellular and humoral immunity, without risking the possibility of insertional mutagenesis, for example. hMPV, PIV, RSV, MeV, BetaCoV (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1) and combinations thereof are referred to herein as "respiratory viruses." Thus, the term "respiratory virus RNA vaccines" encompasses hMPV RNA vaccines, PIV RNA vaccines, RSV RNA vaccines, MeV RNA vaccines, BetaCoV RNA vaccines, and any combination of two or more of hMPV RNA vaccines, PIV RNA vaccines, RSV RNA vaccines, MeV RNA vaccines, and BetaCoV RNA vaccines.

The RNA (e.g., mRNA) vaccines may be utilized in various settings depending on the prevalence of the infection or the degree or level of unmet medical need. The RNA (e.g. mRNA) vaccines may be utilized to treat and/or prevent a hMPV, PIV, RSV, MeV, a BetaCoV (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH, HCoV-HKU1), or any combination of two or more of the foregoing viruses, of various genotypes, strains, and isolates. The RNA (e.g., mRNA) vaccines have superior properties in that they produce much larger antibody titers and produce responses earlier than commercially available anti-viral therapeutic treatments. While not wishing to be bound by theory, it is believed that the RNA (e.g., mRNA) vaccines, as mRNA polynucleotides, are better designed to produce the appropriate protein conformation upon translation as the RNA (e.g., mRNA) vaccines co-opt natural cellular machinery. Unlike traditional vaccines, which are manufactured ex vivo and may trigger unwanted cellular responses, RNA (e.g., mRNA) vaccines are presented to the cellular system in a more native fashion.

In some aspects the invention is a respiratory virus vaccine, comprising at least one RNA polynucleotide having an open reading frame encoding at least one respiratory virus antigenic polypeptide, formulated in a cationic lipid nanoparticle.

Surprisingly, in some aspects, it has also been shown that efficacy of mRNA vaccines can be significantly enhanced when combined with a flagellin adjuvant, in particular, when one or more antigen-encoding mRNAs is combined with an mRNA encoding flagellin.

RNA (e.g., mRNA) vaccines combined with the flagellin adjuvant (e.g., mRNA-encoded flagellin adjuvant) have superior properties in that they may produce much larger antibody titers and produce responses earlier than commercially available vaccine formulations. While not wishing to be bound by theory, it is believed that the RNA (e.g., mRNA) vaccines, for example, as mRNA polynucleotides, are better designed to produce the appropriate protein conformation upon translation, for both the antigen and the adjuvant, as the RNA (e.g., mRNA) vaccines co-opt natural cellular machinery. Unlike traditional vaccines, which are manufactured ex vivo and may trigger unwanted cellular responses, RNA (e.g., mRNA) vaccines are presented to the cellular system in a more native fashion.

Some embodiments of the present disclosure provide RNA (e.g., mRNA) vaccines that include at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one antigenic polypeptide or an immunogenic fragment thereof (e.g., an immunogenic fragment capable of inducing an immune response to the antigenic polypeptide) and at least one RNA (e.g., mRNA polynucleotide) having an open reading frame encoding a flagellin adjuvant.

In some embodiments, at least one flagellin polypeptide (e.g., encoded flagellin polypeptide) is a flagellin protein. In some embodiments, at least one flagellin polypeptide (e.g., encoded flagellin polypeptide) is an immunogenic flagellin fragment. In some embodiments, at least one flagellin polypeptide and at least one antigenic polypeptide are encoded by a single RNA (e.g., mRNA) polynucleotide. In other embodiments, at least one flagellin polypeptide and at least one antigenic polypeptide are each encoded by a different RNA polynucleotide.

In some embodiments at least one flagellin polypeptide has at least 80%, at least 85%, at least 90%, or at least 95% identity to a flagellin polypeptide having a sequence identified by any one of SEQ ID NO: 54-56.

Provided herein, in some embodiments, is a ribonucleic acid (RNA) (e.g., mRNA) vaccine, comprising at least one (e.g., at least 2, 3, 4 or 5) RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one (e.g., at least 2, 3, 4 or 5) hMPV, PIV, RSV, MeV, or a BetaCoV (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH, HCoV-HKU1) antigenic polypeptide, or any combination of two or more of the foregoing antigenic polypeptides. Herein, use of the term "antigenic polypeptide" encompasses immunogenic fragments of the antigenic polypeptide (an immunogenic fragment that is induces (or is capable of inducing) an immune response to hMPV, PIV, RSV, MeV, or a BetaCoV), unless otherwise stated.

Also provided herein, in some embodiments, is a RNA (e.g., mRNA) vaccine comprising at least one (e.g., at least 2, 3, 4 or 5) RNA polynucleotide having an open reading frame encoding at least one (e.g., at least 2, 3, 4 or 5) hMPV, PIV, RSV, MeV, and/or a BetaCoV (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63,

HCoV-NL, HCoV-NH, HCoV-HKU1) antigenic polypeptide or an immunogenic fragment thereof, linked to a signal peptide.

Further provided herein, in some embodiments, is a nucleic acid (e.g., DNA) encoding at least one (e.g., at least 2, 3, 4 or 5) hMPV, PIV, RSV, MeV, and/or a BetaCoV (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH, HCoV-HKU1) RNA (e.g., mRNA) polynucleotide.

Further still, provided herein, in some embodiments, is a method of inducing an immune response in a subject, the method comprising administering to the subject a vaccine comprising at least one (e.g., at least 2, 3, 4 or 5) RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one (e.g., at least 2, 3, 4 or 5) hMPV, PIV, RSV, MeV, and/or a BetaCoV (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH, HCoV-HKU1) antigenic polypeptide, or any combination of two or more of the foregoing antigenic polypeptides.

hMPV/PIV3/RSV

In some embodiments, a RNA (e.g., mRNA) vaccine comprises at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one hMPV, PIV3 or RSV antigenic polypeptide. In some embodiments, at least one antigenic polypeptide is a hMPV, PIV3 or RSV polyprotein. In some embodiments, at least one antigenic polypeptide is major surface glycoprotein G or an immunogenic fragment thereof. In some embodiments, at least one antigenic polypeptide is Fusion (F) glycoprotein (e.g., Fusion glycoprotein F0, F1 or F2) or an immunogenic fragment thereof. In some embodiments, at least one antigenic polypeptide is major surface glycoprotein G or an immunogenic fragment thereof and F glycoprotein or an immunogenic fragment thereof. In some embodiments, the antigenic polypeptide is nucleoprotein (N) or an immunogenic fragment thereof, phosphoprotein (P) or an immunogenic fragment thereof, large polymerase protein (L) or an immunogenic fragment thereof, matrix protein (M) or an immunogenic fragment thereof, small hydrophobic protein (SH) or an immunogenic fragment thereof nonstructural protein1 (NS1) or an immunogenic fragment thereof, or nonstructural protein 2 (NS2) and an immunogenic fragment thereof.

In some embodiments, at least one hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 (Table 3; see also amino acid sequences of Table 4). In some embodiments, the amino acid sequence of the hMPV antigenic polypeptide is, or is a fragment of, or is a homolog or variant having at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) identity to, the amino acid sequence identified by any one of SEQ ID NO: 5-8 (Table 3; see also amino acid sequences of Table 4).

In some embodiments, at least one hMPV antigenic polypeptide is encoded by a nucleic acid sequence identified by any one of SEQ ID NO: 1-4 (Table 2).

In some embodiments, at least one hMPV RNA (e.g., mRNA) polynucleotide is encoded by a nucleic acid sequence, or a fragment of a nucleotide sequence, identified by any one of SEQ ID NO: 1-4 (Table 2). In some embodiments, at least one hMPV RNA (e.g., mRNA) polynucleotide comprises a nucleic acid sequence, or a fragment of a nucleotide sequence, identified by any one of SEQ ID NO: 57-60 (Table 2).

In some embodiments, at least one antigenic polypeptide is obtained from hMPV strain CAN98-75 (CAN75) or the hMPV strain CAN97-83 (CAN83).

In some embodiments, at least one PIV3 antigenic polypeptide comprises hemagglutinin-neuraminidase, Fusion (F) glycoprotein, matrix protein (M), nucleocapsid protein (N), viral replicase (L), non-structural V protein, or an immunogenic fragment thereof.

In some embodiments, at least one PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 (Table 6; see also amino acid sequences of Table 7). In some embodiments, the amino acid sequence of the PIV3 antigenic polypeptide is, or is a fragment of, or is a homolog or variant having at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) identity to, the amino acid sequence identified by any one of SEQ ID NO: 12-13 (Table 6; see also amino acid sequences of Table 7).

In some embodiments, at least one PIV3 antigenic polypeptide is encoded by a nucleic acid sequence identified by any one of SEQ ID NO: 9-12 (Table 5; see also nucleic acid sequences of Table 7).

In some embodiments, at least one PIV3 RNA (e.g., mRNA) polynucleotide is encoded by a nucleic acid sequence, or a fragment of a nucleotide sequence, identified by any one of SEQ ID NO: 9-12 (Table 5; see also nucleic acid sequences of Table 7). In some embodiments, at least one PIV3 RNA (e.g., mRNA) polynucleotide comprises a nucleic acid sequence, or a fragment of a nucleotide sequence, identified by any one of SEQ ID NO: 61-64 (Table 5).

In some embodiments, at least one antigenic polypeptide is obtained from PIV3 strain HPIV3/*Homo sapiens*/PER/FLA4815/2008.

In some embodiments, at least one RSV antigenic polypeptide comprises at least one antigenic polypeptide that comprises glycoprotein G, glycoprotein F, or an immunogenic fragment thereof. In some embodiments, at least one RSV antigenic polypeptide comprises at least one antigenic polypeptide that comprises glycoprotein F and at least one or at least two antigenic polypeptide selected from G, M, N, P, L, SH, M2, NS1 and NS2.

MeV

In some embodiments, a RNA (e.g., mRNA) vaccine comprises at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one MeV antigenic polypeptide. In some embodiments, at least one antigenic polypeptide is a hemagglutinin (HA) protein or an immunogenic fragment thereof. The HA protein may be from MeV strain D3 or B8, for example. In some embodiments, at least one antigenic polypeptide is a Fusion (F) protein or an immunogenic fragment thereof. The F protein may be from MeV strain D3 or B8, for example. In some embodiments, a MeV RNA (e.g., mRNA) vaccines comprises a least one RNA polynucleotide encoding a HA protein and a F protein. The HA and F proteins may be from MeV strain D3 or B8, for example.

In some embodiments, at least one MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 (Table 14). In some embodiments, the amino acid sequence of the MeV antigenic polypeptide is, or is a fragment of, or is a homolog or variant having at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) identity to, the amino acid sequence identified by any one of SEQ ID NO: 47-50 (Table 14).

In some embodiments, at least one MeV antigenic polypeptide is encoded by a nucleic acid sequence of SEQ ID NO: 35-46 (Table 13).

In some embodiments, at least one MeV RNA (e.g., mRNA) polynucleotide is encoded by a nucleic acid sequence, or a fragment of a nucleotide sequence, identified

by any one of SEQ ID NO: 35-46 (Table 13). In some embodiments, at least one MeV RNA (e.g., mRNA) polynucleotide comprises a nucleic acid sequence, or a fragment of a nucleotide sequence, identified by any one of SEQ ID NO: 69-80 (Table 13).

In some embodiments, at least one antigenic polypeptide is obtained from MeV strain B3/B3.1, C2, D4, D6, D7, D8, G3, H1, Moraten, Rubeovax, MVi/New Jersey.USA/45.05, MVi/Texas.USA/4.07, AIK-C, MVi/New York.USA/26.09/3, MVi/California.USA/16.03, MVi/Virginia.USA/15.09, MVi/California.USA/8.04, or MVi/Pennsylvania.USA/20.09.

BetaCoV

In some embodiments, a RNA (e.g., mRNA) vaccine comprises at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one BetaCoV antigenic polypeptide. In some embodiments, the BetaCoV is MERS-CoV. In some embodiments, the BetaCoV is SARS-CoV. In some embodiments, the BetaCoV is HCoV-OC43. In some embodiments, the BetaCoV is HCoV-229E. In some embodiments, the BetaCoV is HCoV-NL63. In some embodiments, the BetaCoV is HCoV-HKU1. In some embodiments, at least one antigenic polypeptide is a betacoronavirus structural protein. For example, a betacoronavirus structural protein may be spike protein (S), envelope protein (E), nucleocapsid protein (N), membrane protein (M) or an immunogenic fragment thereof. In some embodiments, a betacoronavirus structural protein is a spike protein (S). In some embodiments, a betacoronavirus structural protein is a S1 subunit or a S2 subunit of spike protein (S) or an immunogenic fragment thereof.

BetaCoV RNA (e.g., mRNA) polynucleotides of the vaccines provided herein may encode viral protein components of betacoronaviruses, for example, accessory proteins, replicase proteins and the like are encompassed by the present disclosure. RNA (e.g., mRNA) vaccines may include RNA polynucleotides encoding at least one accessory protein (e.g., protein 3, protein 4a, protein 4b, protein 5), at least one replicase protein (e.g., protein 1a, protein 1b), or a combination of at least one accessory protein and at least one replicase protein. The present disclosure also encompasses RNA (e.g., mRNA) vaccines comprising RNA (e.g., mRNA) polynucleotides encoding an accessory protein and/or a replicase protein in combination with at least one structural protein. Due to their surface expression properties, vaccines featuring RNA polynucleotides encoding structural proteins are believed to have preferred immunogenic activity and, hence, may be most suitable for use in the vaccines of the present disclosure.

Some embodiments of the present disclosure provide betacoronavirus (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH, HCoV-HKU1 or a combination thereof) vaccines that include at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one betacoronavirus (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH, HCoV-HKU1) antigenic polypeptide. Also provided herein are pan-betacoronavirus vaccines. Thus, a betacoronavirus vaccine comprising a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding any one, two, three or four of MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, and HCoV-HKU1, for example, may be effective against any one of, any combination of, or all of, MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1. Other betacoronaviruses are encompassed by the present disclosure.

In some embodiments, at least one antigenic polypeptide is a MERS-CoV structural protein. For example, a MERS-CoV structural protein may be spike protein (S), envelope protein (E), nucleocapsid protein (N), membrane protein (M) or an immunogenic fragment thereof. In some embodiments, the MERS-CoV structural protein is a spike protein (S) (see, e.g., Coleman C M et al. *Vaccine* 2014; 32:3169-74, incorporated herein by reference). In some embodiments, the MERS-CoV structural protein is a S1 subunit or a S2 subunit of spike protein (S) or an immunogenic fragment thereof (Li J et al. *Viral Immunol* 2013; 26(2):126-32; He Y et al. *Biochem Biophys Res Commun* 2004; 324(2):773-81, each of which is incorporated herein by reference).

In some embodiments, at least one MERS-CoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-28 or 33 (Table 11). In some embodiments, the amino acid sequence of the MERS-CoV antigenic polypeptide is, or is a fragment of, or is a homolog or variant having at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) identity to, the amino acid sequence identified by any one of SEQ ID NO: 24-28 or 33 (Table 11).

In some embodiments, at least one MERS-CoV antigenic polypeptide is encoded by a nucleic acid sequence identified by any one of SEQ ID NO: 20-23 (Table 10).

In some embodiments, at least one MERS-CoV RNA (e.g., mRNA) polynucleotide is encoded by a nucleic acid sequence, or a fragment of a nucleotide sequence, identified by any one of SEQ ID NO: 20-23 (Table 10). In some embodiments, at least one MERS-CoV RNA (e.g., mRNA) polynucleotide comprises a nucleic acid sequence, or a fragment of a nucleotide sequence, identified by any one of SEQ ID NO: 65-68 (Table 10).

In some embodiments, at least one antigenic polypeptide is obtained from MERS-CoV strain Riyadh_14_2013, 2cEMC/2012, or Hasa_1_2013.

In some embodiments, at least one antigenic polypeptide is a SARS-CoV structural protein. For example, a SARS-CoV structural protein may be spike protein (S), envelope protein (E), nucleocapsid protein (N), membrane protein (M) or an immunogenic fragment thereof. In some embodiments, the SARS-CoV structural protein is a spike protein (S). In some embodiments, the SARS-CoV structural protein is a S1 subunit or a S2 subunit of spike protein (S) or an immunogenic fragment thereof.

In some embodiments, at least one SARS-CoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 29, 32 or 34 (Table 11). In some embodiments, the amino acid sequence of the SARS-CoV antigenic polypeptide is, or is a fragment of, or is a homolog or variant having at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) identity to, the amino acid sequence identified by any one of SEQ ID NO: 29, 32 or 34 (Table 11).

In some embodiments, at least one antigenic polypeptide is a HCoV-OC43 structural protein. For example, a HCoV-OC43 structural protein may be spike protein (S), envelope protein (E), nucleocapsid protein (N), membrane protein (M) or an immunogenic fragment thereof. In some embodiments, the HCoV-OC43 structural protein is a spike protein (S). In some embodiments, the HCoV-OC43 structural protein is a S1 subunit or a S2 subunit of spike protein (S) or an immunogenic fragment thereof.

In some embodiments, at least one HCoV-OC43 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 30 (Table 11). In some embodi-

ments, the amino acid sequence of the HCoV-OC43 antigenic polypeptide is, or is a fragment of, or is a homolog or variant having at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) identity to, the amino acid sequence identified by any one of SEQ ID NO: 30 (Table 11).

In some embodiments, an antigenic polypeptide is a HCoV-HKU1 structural protein. For example, a HCoV-HKU1 structural protein may be spike protein (S), envelope protein (E), nucleocapsid protein (N), membrane protein (M) or an immunogenic fragment thereof. In some embodiments, the HCoV-HKU1 structural protein is a spike protein (S). In some embodiments, the HCoV-HKU1 structural protein is a S1 subunit or a S2 subunit of spike protein (S) or an immunogenic fragment thereof.

In some embodiments, at least one HCoV-HKU1 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 31 (Table 11). In some embodiments, the amino acid sequence of the HCoV-HKU1 antigenic polypeptide is, or is a fragment of, or is a homolog or variant having at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) identity to, the amino acid sequence identified by any one of SEQ ID NO: 31 (Table 11).

In some embodiments, an open reading frame of a RNA (e.g., mRNA) vaccine is codon-optimized. In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, or 47-50 (Tables 3, 6, 11 and 14; see also amino acid sequences of Tables 4, 7, 12 and 15) and is codon optimized mRNA.

In some embodiments, a RNA (e.g., mRNA) vaccine further comprising an adjuvant.

Tables 4, 7, 12 and 15 provide National Center for Biotechnology Information (NCBI) accession numbers of interest. It should be understood that the phrase "an amino acid sequence of Tables 4, 7, 12 and 15" refers to an amino acid sequence identified by one or more NCBI accession numbers listed in Tables 4, 7, 12 and 15. Each of the amino acid sequences, and variants having greater than 95% identity or greater than 98% identity to each of the amino acid sequences encompassed by the accession numbers of Tables 4, 7, 12 and 15 are included within the constructs (polynucleotides/polypeptides) of the present disclosure.

In some embodiments, at least one mRNA polynucleotide is encoded by a nucleic acid having a sequence identified by any one of SEQ ID NO: 1-4, 9-12, 20-23, or 35-46 (Tables 2, 5, 10 and 13; see also nucleic acid sequences of Table 7) and having less than 80% identity to wild-type mRNA sequence. In some embodiments, at least one mRNA polynucleotide is encoded by a nucleic acid having a sequence identified by any one of SEQ ID NO: 1-4, 9-12, 20-23, or 35-46 (Tables 2, 5, 10 and 13; see also nucleic acid sequences of Table 7) and having less than 75%, 85% or 95% identity to a wild-type mRNA sequence. In some embodiments, at least one mRNA polynucleotide is encoded by a nucleic acid having a sequence identified by any one of SEQ ID NO: 1-4, 9-12, 20-23, or 35-46 (Tables 2, 5, 10 and 13; see also nucleic acid sequences of Table 7) and having less than 50-80%, 60-80%, 40-80%, 30-80%, 70-80%, 75-80% or 78-80% identity to wild-type mRNA sequence. In some embodiments, at least one mRNA polynucleotide is encoded by a nucleic acid having a sequence identified by any one of SEQ ID NO: 1-4, 9-12, 20-23, or 35-46 (Tables 2, 5, 10 and 13; see also nucleic acid sequences of Table 7) and having less than 40-85%, 50-85%, 60-85%, 30-85%, 70-85%, 75-85% or 80-85% identity to wild-type mRNA sequence. In some embodiments, at least one mRNA polynucleotide is encoded by a nucleic acid having a sequence identified by any one of SEQ ID NO: 1-4, 9-12, 20-23, or 35-46 (Tables 2, 5, 10 and 13; see also nucleic acid sequences of Table 7) and having less than 40-90%, 50-90%, 60-90%, 30-90%, 70-90%, 75-90%, 80-90%, or 85-90% identity to wild-type mRNA sequence.

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, or 47-50 (Tables 3, 6, 11 and 14; see also amino acid sequences of Tables 4, 7, 12 and 15) and having at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) identity to wild-type mRNA sequence, but does not include wild-type mRNA sequence.

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, or 47-50 (Tables 3, 6, 11 and 14; see also amino acid sequences of Tables 4, 7, 12 and 15) and has less than 95%, 90%, 85%, 80% or 75% identity to wild-type mRNA sequence.

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, or 47-50 (Tables 3, 6, 11 and 14; see also amino acid sequences of Tables 4, 7, 12 and 15) and has 30-80%, 40-80%, 50-80%, 60-80%, 70-80%, 75-80% or 78-80%, 30-85%, 40-85%, 50-805%, 60-85%, 70-85%, 75-85% or 78-85%, 30-90%, 40-90%, 50-90%, 60-90%, 70-90%, 75-90%, 80-90% or 85-90% identity to wild-type mRNA sequence.

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, or 47-50 (Tables 3, 6, 11 and 14; see also amino acid sequences of Tables 4, 7, 12 and 15). In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having 95%-99% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, or 47-50 (Tables 3, 6, 11 and 14; see also amino acid sequences of Tables 4, 7, 12 and 15).

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, or 47-50 (Tables 3, 6, 11 and 14; see also amino acid sequences of Tables 4, 7, 12 and 15) and having membrane fusion activity. In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having 95%-99% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, or 47-50 (Tables 3, 6, 11 and 14; see also amino acid sequences of Tables 4, 7, 12 and 15) and having membrane fusion activity.

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide (e.g., at least one hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one RSV antigenic polypeptide, at least one MeV antigenic polypeptide, or at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides) that attaches to cell receptors.

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide (e.g., at least one

hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one RSV antigenic polypeptide, at least one MeV antigenic polypeptide, or at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides) that causes fusion of viral and cellular membranes.

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide (e.g., at least one hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one RSV antigenic polypeptide, at least one MeV antigenic polypeptide, or at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides) that is responsible for binding of the virus to a cell being infected.

Some embodiments of the present disclosure provide a vaccine that includes at least one ribonucleic acid (RNA) (e.g., mRNA) polynucleotide having an open reading frame encoding at least one antigenic polypeptide (e.g., at least one hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one RSV antigenic polypeptide, at least one MeV antigenic polypeptide, or at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides), at least one 5' terminal cap and at least one chemical modification, formulated within a lipid nanoparticle.

In some embodiments, a 5' terminal cap is 7mG(5')ppp(5')NlmpNp.

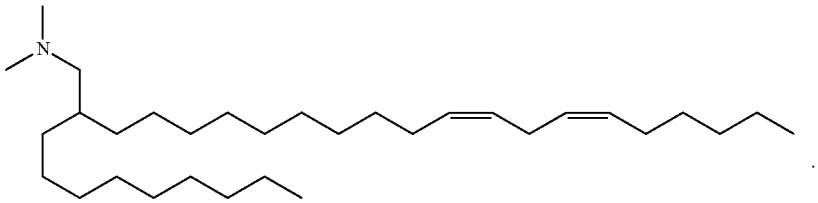
In some embodiments, at least one chemical modification is selected from pseudouridine, N1-methylpseudouridine, N1-ethylpseudouridine, 2-thiouridine, 4'-thiouridine, 5-methylcytosine, 5-methyluridine, 2-thio-1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-pseudouridine, 2-thio-5-aza-uridine, 2-thio-dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-pseudouridine, 4-methoxy-2-thio-pseudouridine, 4-methoxy-pseudouridine, 4-thio-1-methyl-pseudouridine, 4-thio-pseudouridine, 5-aza-uridine, dihydropseudouridine, 5-methoxyuridine and 2'-O-methyl uridine. In some embodiments, the chemical modification is in the 5-position of the uracil. In some embodiments, the chemical modification is a N1-methylpseudouridine. In some embodiments, the chemical modification is a N1-ethylpseudouridine.

In some embodiments, a lipid nanoparticle comprises a cationic lipid, a PEG-modified lipid, a sterol and a non-cationic lipid. In some embodiments, a cationic lipid is an ionizable cationic lipid and the non-cationic lipid is a neutral lipid, and the sterol is a cholesterol. In some embodiments, a cationic lipid is selected from the group consisting of 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), (12Z,15Z)—N,N-dimethyl-2-nonylhenicosa-12,15-dien-1-amine (L608), and N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]heptadecan-8-amine (L530).

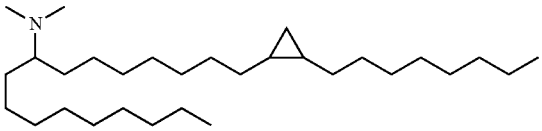
In some embodiments, the lipid is (L608).

In some embodiments, the lipid is

(L608)



(L530)



In some embodiments, a lipid nanoparticle comprises compounds of Formula (I) and/or Formula (II), discussed below.

In some embodiments, a repiratory virus RNA (e.g., mRNA) vaccine is formulated in a lipid nanoparticle that comprises a compound selected from Compounds 3, 18, 20, 25, 26, 29, 30, 60, 108-112 and 122, described below.

Some embodiments of the present disclosure provide a vaccine that includes at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one antigenic polypeptide (e.g., at least one hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one RSV antigenic polypeptide, at least one MeV antigenic polypeptide, or at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides), wherein at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) of the uracil in the open reading frame have a chemical modification, optionally wherein the vaccine is formulated in a lipid nanoparticle (e.g., a lipid nanoparticle comprises a cationic lipid, a PEG-modified lipid, a sterol and a non-cationic lipid).

In some embodiments, 100% of the uracil in the open reading frame have a chemical modification. In some embodiments, a chemical modification is in the 5-position of the uracil. In some embodiments, a chemical modification is a N1-methyl pseudouridine. In some embodiments, 100% of the uracil in the open reading frame have a N1-methyl pseudouridine in the 5-position of the uracil.

In some embodiments, an open reading frame of a RNA (e.g., mRNA) polynucleotide encodes at least two antigenic polypeptides (e.g., at least two hMPV antigenic polypeptides, at least two PIV3 antigenic polypeptides, at least two

RSV antigenic polypeptides, at least two MeV antigenic polypeptides, or at least two BetaCoV antigenic polypeptides, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides). In some embodiments, the open reading frame encodes at least five or at least ten antigenic polypeptides. In some embodiments, the open reading frame encodes at least 100 antigenic polypeptides. In some embodiments, the open reading frame encodes 2-100 antigenic polypeptides.

In some embodiments, a vaccine comprises at least two RNA (e.g., mRNA) polynucleotides, each having an open reading frame encoding at least one antigenic polypeptide (e.g., at least one hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one RSV antigenic polypeptide, at least one MeV antigenic polypeptide, or at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides). In some embodiments, the vaccine comprises at least five or at least ten RNA (e.g., mRNA) polynucleotides, each having an open reading frame encoding at least one antigenic polypeptide or an immunogenic fragment thereof. In some embodiments, the vaccine comprises at least 100 RNA (e.g., mRNA) polynucleotides, each having an open reading frame encoding at least one antigenic polypeptide. In some embodiments, the vaccine comprises 2-100 RNA (e.g., mRNA) polynucleotides, each having an open reading frame encoding at least one antigenic polypeptide.

In some embodiments, at least one antigenic polypeptide (e.g., at least one hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one RSV antigenic polypeptide, at least one MeV antigenic polypeptide, or at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides) is fused to a signal peptide. In some embodiments, the signal peptide is selected from: a HuIgGk signal peptide (METPAQLLFLLLLWLPDTTG; SEQ ID NO: 15); IgE heavy chain epsilon-1 signal peptide (MDWTWIL-FLVAAATRVHS; SEQ ID NO: 16); Japanese encephalitis PRM signal sequence (MLGSNSGQRVVFTILLLLVA-PAYS; SEQ ID NO: 17), VSVg protein signal sequence (MKCLLYLAFLFIGVNCA; SEQ ID NO: 18) and Japanese encephalitis JEV signal sequence (MWLVSLAIVTA-CAGA; SEQ ID NO: 19).

In some embodiments, the signal peptide is fused to the N-terminus of at least one antigenic polypeptide. In some embodiments, a signal peptide is fused to the C-terminus of at least one antigenic polypeptide.

In some embodiments, at least one antigenic polypeptide (e.g., at least one hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one RSV antigenic polypeptide, at least one MeV antigenic polypeptide, or at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides) comprises a mutated N-linked glycosylation site.

Also provided herein is a RNA (e.g., mRNA) vaccine of any one of the foregoing paragraphs (e.g., a hMPV vaccine, a PIV3 vaccine, a RSV vaccine, a MeV vaccine, or a BetaCoV vaccine, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing vaccines), formulated in a nanoparticle (e.g., a lipid nanoparticle).

In some embodiments, the nanoparticle has a mean diameter of 50-200 nm. In some embodiments, the nanoparticle is a lipid nanoparticle. In some embodiments, the lipid nanoparticle comprises a cationic lipid, a PEG-modified lipid, a sterol and a non-cationic lipid. In some embodiments, the lipid nanoparticle comprises a molar ratio of about 20-60% cationic lipid, 0.5-15% PEG-modified lipid, 25-55% sterol, and 25% non-cationic lipid. In some embodiments, the cationic lipid is an ionizable cationic lipid and the non-cationic lipid is a neutral lipid, and the sterol is a cholesterol. In some embodiments, the cationic lipid is selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319).

In some embodiments, a lipid nanoparticle comprises compounds of Formula (I) and/or Formula (II), as discussed below.

In some embodiments, a lipid nanoparticle comprises Compounds 3, 18, 20, 25, 26, 29, 30, 60, 108-112, or 122, as discussed below.

In some embodiments, the nanoparticle has a polydispersity value of less than 0.4 (e.g., less than 0.3, 0.2 or 0.1).

In some embodiments, the nanoparticle has a net neutral charge at a neutral pH value.

In some embodiments, the respiratory virus vaccine is multivalent.

Some embodiments of the present disclosure provide methods of inducing an antigen specific immune response in a subject, comprising administering to the subject any of the RNA (e.g., mRNA) vaccine as provided herein in an amount effective to produce an antigen-specific immune response. In some embodiments, the RNA (e.g., mRNA) vaccine is a hMPV vaccine, a PIV3 vaccine, a RSV vaccine, a MeV vaccine, or a BetaCoV vaccine, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1 vaccines. In some embodiments, the RNA (e.g., mRNA) vaccine is a combination vaccine comprising a combination of any two or more of the foregoing vaccines.

In some embodiments, an antigen-specific immune response comprises a T cell response or a B cell response.

In some embodiments, a method of producing an antigen-specific immune response comprises administering to a subject a single dose (no booster dose) of a RNA (e.g., mRNA) vaccine of the present disclosure. In some embodiments, the RNA (e.g., mRNA) vaccine is a hMPV vaccine, a PIV3 vaccine, a RSV vaccine, a MeV vaccine, or a BetaCoV vaccine, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1 vaccines. In some embodiments, the RNA (e.g., mRNA) vaccine is a combination vaccine comprising a combination of any two or more of the foregoing vaccines.

In some embodiments, a method further comprises administering to the subject a second (booster) dose of a RNA (e.g., mRNA) vaccine. Additional doses of a RNA (e.g., mRNA) vaccine may be administered.

In some embodiments, the subjects exhibit a seroconversion rate of at least 80% (e.g., at least 85%, at least 90%, or at least 95%) following the first dose or the second (booster)

dose of the vaccine. Seroconversion is the time period during which a specific antibody develops and becomes detectable in the blood. After seroconversion has occurred, a virus can be detected in blood tests for the antibody. During an infection or immunization, antigens enter the blood, and the immune system begins to produce antibodies in response. Before seroconversion, the antigen itself may or may not be detectable, but antibodies are considered absent. During seroconversion, antibodies are present but not yet detectable. Any time after seroconversion, the antibodies can be detected in the blood, indicating a prior or current infection.

In some embodiments, a RNA (e.g., mRNA) vaccine is administered to a subject by intradermal or intramuscular injection.

Some embodiments, of the present disclosure provide methods of inducing an antigen specific immune response in a subject, including administering to a subject a RNA (e.g., mRNA) vaccine in an effective amount to produce an antigen specific immune response in a subject. Antigen-specific immune responses in a subject may be determined, in some embodiments, by assaying for antibody titer (for titer of an antibody that binds to a hMPV, PIV3, RSV, MeV and/or BetaCoV antigenic polypeptide) following administration to the subject of any of the RNA (e.g., mRNA) vaccines of the present disclosure. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased by at least 1 log relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased by 1-3 log relative to a control.

In some embodiments, the anti-antigenic polypeptide antibody titer produced in a subject is increased at least 2 times relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased at least 5 times relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased at least 10 times relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased 2-10 times relative to a control.

In some embodiments, the control is an anti-antigenic polypeptide antibody titer produced in a subject who has not been administered a RNA (e.g., mRNA) vaccine of the present disclosure. In some embodiments, the control is an anti-antigenic polypeptide antibody titer produced in a subject who has been administered a live attenuated or inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine (see, e.g., Ren J. et al. *J of Gen. Virol.* 2015; 96: 1515-1520), or wherein the control is an anti-antigenic polypeptide antibody titer produced in a subject who has been administered a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine. In some embodiments, the control is an anti-antigenic polypeptide antibody titer produced in a subject who has been administered a hMPV, PIV3, RSV, MeV and/or BetaCoV virus-like particle (VLP) vaccine (see, e.g., Cox R G et al., *J Virol.* 2014 June; 88(11): 6368-6379).

A RNA (e.g., mRNA) vaccine of the present disclosure is administered to a subject in an effective amount (an amount effective to induce an immune response). In some embodiments, the effective amount is a dose equivalent to an at least 2-fold, at least 4-fold, at least 10-fold, at least 100-fold, at least 1000-fold reduction in the standard of care dose of a recombinant hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine, wherein the anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine, a purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine, a live attenuated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine, an inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine, or a hMPV, PIV3, RSV, MeV and/or BetaCoV VLP vaccine. In some embodiments, the effective amount is a dose equivalent to 2-1000-fold reduction in the standard of care dose of a recombinant hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine, wherein the anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine, a purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine, a live attenuated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine, an inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine, or a hMPV, PIV3, RSV, MeV and/or BetaCoV VLP vaccine.

In some embodiments, the control is an anti-antigenic polypeptide antibody titer produced in a subject who has been administered a virus-like particle (VLP) vaccine comprising structural proteins of hMPV, PIV3, RSV, MeV and/or BetaCoV.

In some embodiments, the RNA (e.g., mRNA) vaccine is formulated in an effective amount to produce an antigen specific immune response in a subject.

In some embodiments, the effective amount is a total dose of 25 μg to 1000 μg, or 50 μg to 1000 μg. In some embodiments, the effective amount is a total dose of 100 μg. In some embodiments, the effective amount is a dose of 25 μg administered to the subject a total of two times. In some embodiments, the effective amount is a dose of 100 μg administered to the subject a total of two times. In some embodiments, the effective amount is a dose of 400 μg administered to the subject a total of two times. In some embodiments, the effective amount is a dose of 500 μg administered to the subject a total of two times.

In some embodiments, the efficacy (or effectiveness) of a RNA (e.g., mRNA) vaccine is greater than 60%. In some embodiments, the RNA (e.g., mRNA) polynucleotide of the vaccine at least one hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one RSV antigenic polypeptide, at least one MeV antigenic polypeptide, at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides.

Vaccine efficacy may be assessed using standard analyses (see, e.g., Weinberg et al., *J Infect Dis.* 2010 Jun. 1; 201(11):1607-10). For example, vaccine efficacy may be measured by double-blind, randomized, clinical controlled trials. Vaccine efficacy may be expressed as a proportionate reduction in disease attack rate (AR) between the unvaccinated (ARU) and vaccinated (ARV) study cohorts and can be calculated from the relative risk (RR) of disease among the vaccinated group with use of the following formulas:

$$\text{Efficacy}=(\text{ARU}-\text{ARV})/\text{ARU}\times 100; \text{ and}$$

$$\text{Efficacy}=(1-\text{RR})\times 100.$$

Likewise, vaccine effectiveness may be assessed using standard analyses (see, e.g., Weinberg et al., *J Infect Dis.* 2010 Jun. 1; 201(11):1607-10). Vaccine effectiveness is an

assessment of how a vaccine (which may have already proven to have high vaccine efficacy) reduces disease in a population. This measure can assess the net balance of benefits and adverse effects of a vaccination program, not just the vaccine itself, under natural field conditions rather than in a controlled clinical trial. Vaccine effectiveness is proportional to vaccine efficacy (potency) but is also affected by how well target groups in the population are immunized, as well as by other non-vaccine-related factors that influence the 'real-world' outcomes of hospitalizations, ambulatory visits, or costs. For example, a retrospective case control analysis may be used, in which the rates of vaccination among a set of infected cases and appropriate controls are compared. Vaccine effectiveness may be expressed as a rate difference, with use of the odds ratio (OR) for developing infection despite vaccination:

$$\text{Effectiveness}=(1-\text{OR})\times 100.$$

In some embodiments, the efficacy (or effectiveness) of a RNA (e.g., mRNA) vaccine is at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, or at least 90%.

In some embodiments, the vaccine immunizes the subject against hMPV, PIV3, RSV, MeV, BetaCoV (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1), or any combination of two or more of the foregoing viruses for up to 2 years. In some embodiments, the vaccine immunizes the subject against hMPV, PIV3, RSV, MeV, BetaCoV (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1), or any combination of two or more of the foregoing viruses for more than 2 years, more than 3 years, more than 4 years, or for 5-10 years.

In some embodiments, the subject is about 5 years old or younger. For example, the subject may be between the ages of about 1 year and about 5 years (e.g., about 1, 2, 3, 5 or 5 years), or between the ages of about 6 months and about 1 year (e.g., about 6, 7, 8, 9, 10, 11 or 12 months). In some embodiments, the subject is about 12 months or younger (e.g., 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 months or 1 month). In some embodiments, the subject is about 6 months or younger.

In some embodiments, the subject was born full term (e.g., about 37-42 weeks). In some embodiments, the subject was born prematurely, for example, at about 36 weeks of gestation or earlier (e.g., about 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26 or 25 weeks). For example, the subject may have been born at about 32 weeks of gestation or earlier. In some embodiments, the subject was born prematurely between about 32 weeks and about 36 weeks of gestation. In such subjects, a RNA (e.g., mRNA) vaccine may be administered later in life, for example, at the age of about 6 months to about 5 years, or older.

In some embodiments, the subject is pregnant (e.g., in the first, second or third trimester) when administered an RNA (e.g., mRNA) vaccine. Viruses such as hMPV, PIV3 and RSV causes infections of the lower respiratory tract, mainly in infants and young children. One-third of RSV related deaths, for example, occur in the first year of life, with 99 percent of these deaths occurring in low-resource countries. It's so widespread in the United States that nearly all children become infected with the virus before their second birthdays. Thus, the present disclosure provides RNA (e.g., mRNA) vaccines for maternal immunization to improve mother-to-child transmission of protection against the virus.

In some embodiments, the subject is a young adult between the ages of about 20 years and about 50 years (e.g., about 20, 25, 30, 35, 40, 45 or 50 years old).

In some embodiments, the subject is an elderly subject about 60 years old, about 70 years old, or older (e.g., about 60, 65, 70, 75, 80, 85 or 90 years old).

In some embodiments, the subject is has a chronic pulmonary disease (e.g., chronic obstructive pulmonary disease (COPD) or asthma). Two forms of COPD include chronic bronchitis, which involves a long-term cough with mucus, and emphysema, which involves damage to the lungs over time. Thus, a subject administered a RNA (e.g., mRNA) vaccine may have chronic bronchitis or emphysema.

In some embodiments, the subject has been exposed to hMPV, PIV3, RSV, MeV, BetaCoV (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1), or any combination of two or more of the foregoing viruses; the subject is infected with hMPV, PIV3, RSV, MeV, BetaCoV (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1), or any combination of two or more of the foregoing viruses; or subject is at risk of infection by hMPV, PIV3, RSV, MeV, BetaCoV (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1), or any combination of two or more of the foregoing viruses.

In some embodiments, the subject is immunocompromised (has an impaired immune system, e.g., has an immune disorder or autoimmune disorder).

In some embodiments the nucleic acid vaccines described herein are chemically modified. In other embodiments the nucleic acid vaccines are unmodified.

Yet other aspects provide compositions for and methods of vaccinating a subject comprising administering to the subject a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding a first respiratory virus antigenic polypeptide, wherein the RNA polynucleotide does not include a stabilization element, and wherein an adjuvant is not coformulated or co-administered with the vaccine.

In other aspects the invention is a composition for or method of vaccinating a subject comprising administering to the subject a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding a first antigenic polypeptide wherein a dosage of between 10 μg/kg and 400 μg/kg of the nucleic acid vaccine is administered to the subject. In some embodiments the dosage of the RNA polynucleotide is 1-5 μg, 5-10 μg, 10-15 μg, 15-20 μg, 10-25 μg, 20-25 μg, 20-50 μg, 30-50 μg, 40-50 μg, 40-60 μg, 60-80 μg, 60-100 μg, 50-100 μg, 80-120 μg, 40-120 μg, 40-150 μg, 50-150 μg, 50-200 μg, 80-200 μg, 100-200 μg, 120-250 μg, 150-250 μg, 180-280 μg, 200-300 μg, 50-300 μg, 80-300 μg, 100-300 μg, 40-300 μg, 50-350 μg, 100-350 μg, 200-350 μg, 300-350 μg, 320-400 μg, 40-380 μg, 40-100 μg, 100-400 μg, 200-400 μg, or 300-400 μg per dose. In some embodiments, the nucleic acid vaccine is administered to the subject by intradermal or intramuscular injection. In some embodiments, the nucleic acid vaccine is administered to the subject on day zero. In some embodiments, a second dose of the nucleic acid vaccine is administered to the subject on day twenty one.

In some embodiments, a dosage of 25 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some embodiments, a dosage of 100 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some

embodiments, a dosage of 50 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some embodiments, a dosage of 75 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some embodiments, a dosage of 150 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some embodiments, a dosage of 400 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some embodiments, a dosage of 200 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some embodiments, the RNA polynucleotide accumulates at a 100 fold higher level in the local lymph node in comparison with the distal lymph node. In other embodiments the nucleic acid vaccine is chemically modified and in other embodiments the nucleic acid vaccine is not chemically modified.

Aspects of the invention provide a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding a first antigenic polypeptide, wherein the RNA polynucleotide does not include a stabilization element, and a pharmaceutically acceptable carrier or excipient, wherein an adjuvant is not included in the vaccine. In some embodiments, the stabilization element is a histone stem-loop. In some embodiments, the stabilization element is a nucleic acid sequence having increased GC content relative to wild type sequence.

Aspects of the invention provide nucleic acid vaccines comprising one or more RNA polynucleotides having an open reading frame encoding a first antigenic polypeptide, wherein the RNA polynucleotide is present in the formulation for in vivo administration to a host, which confers an antibody titer superior to the criterion for seroprotection for the first antigen for an acceptable percentage of human subjects. In some embodiments, the antibody titer produced by the mRNA vaccines of the invention is a neutralizing antibody titer. In some embodiments the neutralizing antibody titer is greater than a protein vaccine. In other embodiments the neutralizing antibody titer produced by the mRNA vaccines of the invention is greater than an adjuvanted protein vaccine. In yet other embodiments the neutralizing antibody titer produced by the mRNA vaccines of the invention is 1,000-10,000, 1,200-10,000, 1,400-10,000, 1,500-10,000, 1,000-5,000, 1,000-4,000, 1,800-10,000, 2000-10,000, 2,000-5,000, 2,000-3,000, 2,000-4,000, 3,000-5,000, 3,000-4,000, or 2,000-2,500. A neutralization titer is typically expressed as the highest serum dilution required to achieve a 50% reduction in the number of plaques.

Also provided are nucleic acid vaccines comprising one or more RNA polynucleotides having an open reading frame encoding a first antigenic polypeptide, wherein the RNA polynucleotide is present in a formulation for in vivo administration to a host for eliciting a longer lasting high antibody titer than an antibody titer elicited by an mRNA vaccine having a stabilizing element or formulated with an adjuvant and encoding the first antigenic polypeptide. In some embodiments, the RNA polynucleotide is formulated to produce a neutralizing antibodies within one week of a single administration. In some embodiments, the adjuvant is selected from a cationic peptide and an immunostimulatory nucleic acid. In some embodiments, the cationic peptide is protamine.

Aspects provide nucleic acid vaccines comprising one or more RNA polynucleotides having an open reading frame comprising at least one chemical modification or optionally no nucleotide modification, the open reading frame encoding a first antigenic polypeptide, wherein the RNA polynucleotide is present in the formulation for in vivo administration to a host such that the level of antigen expression in the host significantly exceeds a level of antigen expression produced by an mRNA vaccine having a stabilizing element or formulated with an adjuvant and encoding the first antigenic polypeptide.

Other aspects provide nucleic acid vaccines comprising one or more RNA polynucleotides having an open reading frame comprising at least one chemical modification or optionally no nucleotide modification, the open reading frame encoding a first antigenic polypeptide, wherein the vaccine has at least 10 fold less RNA polynucleotide than is required for an unmodified mRNA vaccine to produce an equivalent antibody titer. In some embodiments, the RNA polynucleotide is present in a dosage of 25-100 micrograms.

Aspects of the invention also provide a unit of use vaccine, comprising between 10 ug and 400 ug of one or more RNA polynucleotides having an open reading frame comprising at least one chemical modification or optionally no nucleotide modification, the open reading frame encoding a first antigenic polypeptide, and a pharmaceutically acceptable carrier or excipient, formulated for delivery to a human subject. In some embodiments, the vaccine further comprises a cationic lipid nanoparticle.

Aspects of the invention provide methods of creating, maintaining or restoring antigenic memory to a respiratory virus strain in an individual or population of individuals comprising administering to said individual or population an antigenic memory booster nucleic acid vaccine comprising (a) at least one RNA polynucleotide, said polynucleotide comprising at least one chemical modification or optionally no nucleotide modification and two or more codon-optimized open reading frames, said open reading frames encoding a set of reference antigenic polypeptides, and (b) optionally a pharmaceutically acceptable carrier or excipient. In some embodiments, the vaccine is administered to the individual via a route selected from the group consisting of intramuscular administration, intradermal administration and subcutaneous administration. In some embodiments, the administering step comprises contacting a muscle tissue of the subject with a device suitable for injection of the composition. In some embodiments, the administering step comprises contacting a muscle tissue of the subject with a device suitable for injection of the composition in combination with electroporation.

Aspects of the invention provide methods of vaccinating a subject comprising administering to the subject a single dosage of between 25 ug/kg and 400 ug/kg of a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding a first antigenic polypeptide in an effective amount to vaccinate the subject.

Other aspects provide nucleic acid vaccines comprising one or more RNA polynucleotides having an open reading frame comprising at least one chemical modification, the open reading frame encoding a first antigenic polypeptide, wherein the vaccine has at least 10 fold less RNA polynucleotide than is required for an unmodified mRNA vaccine to produce an equivalent antibody titer. In some embodiments, the RNA polynucleotide is present in a dosage of 25-100 micrograms.

Other aspects provide nucleic acid vaccines comprising an LNP formulated RNA polynucleotide having an open reading frame comprising no nucleotide modifications (unmodified), the open reading frame encoding a first antigenic polypeptide, wherein the vaccine has at least 10 fold less RNA polynucleotide than is required for an unmodified

mRNA vaccine not formulated in a LNP to produce an equivalent antibody titer. In some embodiments, the RNA polynucleotide is present in a dosage of 25-100 micrograms.

The data presented in the Examples demonstrate significant enhanced immune responses using the formulations of the invention. Both chemically modified and unmodified RNA vaccines are useful according to the invention. Surprisingly, in contrast to prior art reports that it was preferable to use chemically unmodified mRNA formulated in a carrier for the production of vaccines, it is described herein that chemically modified mRNA-LNP vaccines required a much lower effective mRNA dose than unmodified mRNA, i.e., tenfold less than unmodified mRNA when formulated in carriers other than LNP. Both the chemically modified and unmodified RNA vaccines of the invention produce better immune responses than mRNA vaccines formulated in a different lipid carrier.

In other aspects the invention encompasses a method of treating an elderly subject age 60 years or older comprising administering to the subject a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding a respiratory virus antigenic polypeptide in an effective amount to vaccinate the subject.

In other aspects the invention encompasses a method of treating a young subject age 17 years or younger comprising administering to the subject a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding a respiratory virus antigenic polypeptide in an effective amount to vaccinate the subject.

In other aspects the invention encompasses a method of treating an adult subject comprising administering to the subject a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding a respiratory virus antigenic polypeptide in an effective amount to vaccinate the subject.

In some aspects the invention is a method of vaccinating a subject with a combination vaccine including at least two nucleic acid sequences encoding respiratory antigens wherein the dosage for the vaccine is a combined therapeutic dosage wherein the dosage of each individual nucleic acid encoding an antigen is a sub therapeutic dosage. In some embodiments, the combined dosage is 25 micrograms of the RNA polynucleotide in the nucleic acid vaccine administered to the subject. In some embodiments, the combined dosage is 100 micrograms of the RNA polynucleotide in the nucleic acid vaccine administered to the subject. In some embodiments the combined dosage is 50 micrograms of the RNA polynucleotide in the nucleic acid vaccine administered to the subject. In some embodiments, the combined dosage is 75 micrograms of the RNA polynucleotide in the nucleic acid vaccine administered to the subject. In some embodiments, the combined dosage is 150 micrograms of the RNA polynucleotide in the nucleic acid vaccine administered to the subject. In some embodiments, the combined dosage is 400 micrograms of the RNA polynucleotide in the nucleic acid vaccine administered to the subject. In some embodiments, the sub therapeutic dosage of each individual nucleic acid encoding an antigen is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 micrograms. In other embodiments the nucleic acid vaccine is chemically modified and in other embodiments the nucleic acid vaccine is not chemically modified.

The RNA polynucleotide is one of SEQ ID NO: 1-4, 9-12, 20-23, 35-46, 57-61, and 64-80 and includes at least one chemical modification. In other embodiments the RNA polynucleotide is one of SEQ ID NO: 1-4, 9-12, 20-23, 35-46, 57-61, and 64-80 and does not include any nucleotide modifications, or is unmodified. In yet other embodiments the at least one RNA polynucleotide encodes an antigenic protein of any of SEQ ID NO: 5-8, 12-13, 24-34, and 47-50 and includes at least one chemical modification. In other embodiments the RNA polynucleotide encodes an antigenic protein of any of SEQ ID NO: 5-8, 12-13, 24-34, and 47-50 and does not include any nucleotide modifications, or is unmodified.

In preferred aspects, vaccines of the invention (e.g., LNP-encapsulated mRNA vaccines) produce prophylactically- and/or therapeutically-efficacious levels, concentrations and/or titers of antigen-specific antibodies in the blood or serum of a vaccinated subject. As defined herein, the term antibody titer refers to the amount of antigen-specific antibody produces in s subject, e.g., a human subject. In exemplary embodiments, antibody titer is expressed as the inverse of the greatest dilution (in a serial dilution) that still gives a positive result. In exemplary embodiments, antibody titer is determined or measured by enzyme-linked immunosorbent assay (ELISA). In exemplary embodiments, antibody titer is determined or measured by neutralization assay, e.g., by microneutralization assay. In certain aspects, antibody titer measurement is expressed as a ratio, such as 1:40, 1:100, etc. In exemplary embodiments of the invention, an efficacious vaccine produces an antibody titer of greater than 1:40, greater that 1:100, greater than 1:400, greater than 1:1000, greater than 1:2000, greater than 1:3000, greater than 1:4000, greater than 1:500, greater than 1:6000, greater than 1:7500, greater than 1:10000. In exemplary embodiments, the antibody titer is produced or reached by 10 days following vaccination, by 20 days following vaccination, by 30 days following vaccination, by 40 days following vaccination, or by 50 or more days following vaccination. In exemplary embodiments, the titer is produced or reached following a single dose of vaccine administered to the subject. In other embodiments, the titer is produced or reached following multiple doses, e.g., following a first and a second dose (e.g., a booster dose.) In exemplary aspects of the invention, antigen-specific antibodies are measured in units of μg/ml or are measured in units of IU/L (International Units per liter) or mIU/ml (milli International Units per ml). In exemplary embodiments of the invention, an efficacious vaccine produces >0.5 μg/ml, >0.1 μg/ml, >0.2 μg/ml, >0.35 μg/ml, >0.5 μg/ml, >1 μg/ml, >2 μg/ml, >5 μg/ml or >10 μg/ml. In exemplary embodiments of the invention, an efficacious vaccine produces >10 mIU/ml, >20 mIU/ml, >50 mIU/ml, >100 mIU/ml, >200 mIU/ml, >500 mIU/ml or >1000 mIU/ml. In exemplary embodiments, the antibody level or concentration is produced or reached by 10 days following vaccination, by 20 days following vaccination, by 30 days following vaccination, by 40 days following vaccination, or by 50 or more days following vaccination. In exemplary embodiments, the level or concentration is produced or reached following a single dose of vaccine administered to the subject. In other embodiments, the level or concentration is produced or reached following multiple doses, e.g., following a first and a second dose (e.g., a booster dose.) In exemplary embodiments, antibody level or concentration is determined or measured by enzyme-linked immunosorbent assay (ELISA). In exemplary embodiments, antibody level or concentration is determined or measured by neutralization assay, e.g., by microneutralization assay.

The details of various embodiments of the disclosure are set forth in the description below. Other features, objects,

and advantages of the disclosure will be apparent from the description and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other objects, features and advantages will be apparent from the following description of particular embodiments of the disclosure, as illustrated in the accompanying drawings in which like reference characters refer to the same parts throughout the different views. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating the principles of various embodiments of the disclosure.

FIG. **1** shows a schematic of one example of a RNA (e.g. mRNA) vaccine construct of the present disclosure. The construct depicts a human metapneumovirus and human respiratory syncytial virus full length fusion protein obtained from wild-type strains (*The Journal of General Virology*. 2008; 89(Pt 12):3113-3118, incorporated herein by reference).

FIGS. **2**A-**2**C are graphs showing the levels of anti-hMPV fusion protein-specific antibodies in the serum of mice immunized with hMPV mRNA vaccines on day 0 (FIG. **2**A), day 14 (FIG. **2**B) and day 35 (FIG. **2**C) post immunization. The mice were immunized with a single dose (2 μg or 10 μg) on day 0 and were given a boost dose (2 μg or 10 μg) on day 21. hMPV fusion protein-specific antibodies were detected at up to 1:10000 dilution of serum on day 35 for both doses.

FIGS. **3**A-**3**C are graphs showing the result of IgG isotyping in the serum of mice immunized with hMPV mRNA vaccines. The levels of hMPV fusion protein-specific IgG2a (FIG. **3**A) and IgG1 (FIG. **3**B) antibodies in the serum are measured by ELISA. FIG. **3**C shows that hMPV fusion protein mRNA vaccine induced a mixed Th1/Th2 cytokine response with a Th1 bias.

FIG. **4** is a graph showing in vitro neutralization of a hMPV B2 strain (TN/91-316) using the sera of mice immunized with a mRNA vaccine encoding hMPV fusion protein. Mouse serum obtained from mice receiving a 10 μg or a 2 μg dose contained hMPV-neutralizing antibodies.

FIGS. **5**A-**5**C are graphs showing a Th1 cytokine response induced by a hMPV fusion peptide pool (15-mers-50 (overlap)) in splenocytes isolated from mice immunized with the hMPV mRNA vaccines. Virus-free media was used as a negative control and Concanavalin A (ConA, a positive control for splenocyte stimulation) was included. The cytokines tested included IFN-γ (FIG. **5**A), IL-2 (FIG. **5**B) and IL12 (FIG. **5**C).

FIGS. **6**A-**6**E are graphs showing the Th2 cytokine response induced by a hMPV fusion peptide pool (15-mers-50) in splenocytes isolated from mice immunized with the hMPV mRNA vaccines. Virus-free media was used as a negative control and Concanavalin A was also included. The cytokines tested included IL-10 (FIG. **6**A), TNF-α (FIG. **6**B), IL4 (FIG. **6**C), IL-5 (FIG. **6**D) and IL-6 (FIG. **6**E).

FIGS. **7**A-**7**C are graphs showing the Th1 response induced by inactivated hMPV virus in splenocytes isolated from mice immunized with hMPV mRNA vaccines. Virus-free media was used as a negative control and Concanavalin A was included. The cytokines tested included IFN-γ (FIG. **7**A), IL-2 (FIG. **7**B) and IL12 (FIG. **7**C).

FIGS. **8**A-**8**E are graphs showing the Th2 response induced by inactivated hMPV virus in splenocytes isolated from mice immunized with the hMPV mRNA vaccines. Virus-free media was used as a negative control and Concanavalin A was included. The cytokines tested include IL-10 (FIG. **8**A), TNF-α (FIG. **8**B), IL4 (FIG. **8**C), IL-5 (FIG. **8**D) and IL-6 (FIG. **8**E).

FIGS. **9**A-**9**B are graphs showing the results of cotton rat challenge experiments. Two different doses of the hMPV mRNA vaccines were used (2 μg or 10 μg doses) to immunize the cotton rats before challenge. The hMPV mRNA vaccines reduced the viral titer in the lung and nose of the cotton rat, with the 10 μg dose being more effective in reducing viral titer. Use of a 10 μg dose resulted in 100% protection in the lung and a ~2 log reduction in nose viral titer. Use of a 2 μg dose resulted in a 1 log reduction in lung vital titer and no reduction in nose viral titer. The vaccine was administered on Day 0, and a boost was administered on Day 21.

FIG. **10** is a graph showing the lung histopathology of cotton rats that received hMPV mRNA vaccines. Pathology associated with vaccine-enhanced disease was not observed in immunized groups.

FIG. **11** is a graph showing hMPV neutralization antibody titers in cotton rats that received hMPV mRNA vaccines (2 μg or 10 μg doses) on days 35 and 42 post immunization.

FIG. **12** is a graph showing the lung and nose viral load in cotton rats challenged with a hMPV/A2 strain after immunization with the indicated mRNA vaccines (hMPV mRNA vaccine or hMPV/PIV mRNA combination vaccine). Vaccinated cotton rats showed reduced lung and nose viral loads after challenge, compared to control.

FIG. **13** is a graph showing the lung and nose viral load in cotton rats challenged with PIV3 strain after immunization with indicated mRNA vaccines (PIV mRNA vaccine or hMPV/PIV combination vaccine). Vaccinated cotton rats showed reduced lung and nose viral loads after challenge, compared to control.

FIG. **14** is a graph showing hMPV neutralizing antibody titers in cotton rats that received different dosages of hMPV mRNA vaccines or hMPV/PIV combination mRNA vaccines on day 42 post immunization. The dosages of the vaccine are indicated in Table 9.

FIG. **15** is a graph showing PIV3 neutralizing antibody titers in cotton rats that received different dosages of PIV mRNA vaccines or hMPV/PIV combination mRNA vaccines on day 42 post immunization. The dosages of the vaccine are indicated in Table 9.

FIG. **16** is a graph showing the lung histopathology score of cotton rats immunized with hMPV mRNA vaccines, PIV mRNA vaccines or hMPV/PIV combination mRNA vaccines as indicated in Table 9. Low occurrence of alevolitis and interstitial pneumonia was observed, indicating no antibody-dependent enhancement (ADE) of hMPV associated diseases.

FIG. **17** is a graph showing the reciprocal MERS-CoV neutralizing antibody titers in mice immunized with beta-coronavirus mRNA vaccine encoding the MERS-CoV full-length Spike protein, on days 0, 21, 42, and 56 post immunization.

FIG. **18** is a graph showing the reciprocal MERS-CoV neutralizing antibody titers in mice immunized with beta-coronavirus mRNA vaccine encoding either the MERS-CoV full-length Spike protein, or the S2 subunit of the Spike protein. The full length spike protein induced a stronger immune response compared to the S2 subunit alone.

FIGS. **19**A-**19**C are graphs showing the viral load in the nose and throat, the bronchoalveolar lavage (BAL), or the lungs of New Zealand white rabbits 4 days post challenge with MERS-CoV. The New Zealand white rabbits were immunized with one 20 μg-dose (on day 0) or two 20 μg-doses (on day 0 and 21) of MERS-CoV mRNA vaccine

encoding the full-length Spike protein before challenge. FIG. **19**A shows that two doses of MERS-CoV mRNA vaccine resulted in a 3 log reduction of viral load in the nose and led to complete protection in the throat of the New Zealand white rabbits. FIG. **19**B shows that two doses of MERS-CoV mRNA vaccine resulted in a 4 log reduction of viral load in the BAL of the New Zealand white rabbits. FIG. **19**C show one dose of MERS-CoV mRNA vaccine resulted in a 2 log reduction of viral load, while two doses of MERS-CoV mRNA vaccine resulted in an over 4 log reduction of viral load in the lungs of the New Zealand white rabbits.

FIGS. **20**A-**20**B are images and graphs showing viral load or replicating virus detected by PCR in the lungs of New Zealand white rabbits 4 days post challenge with MERS-CoV. The New Zealand white rabbits were immunized with a single 20 μg dose (on day 0, Group 1a) of MERS-CoV mRNA vaccine encoding the full-length Spike protein, two 20 μg doses (on day 0 and 21, Group 1b) of MERS-CoV mRNA vaccine encoding the full-length Spike protein, or placebo (Group 2) before challenge. FIG. **20**A shows that two doses of 20 μg a MERS-CoV mRNA vaccine reduced over 99% (2 log) of viruses in the lungs of New Zealand white rabbits. FIG. **20**B shows that the group of New Zealand white rabbits that received 2 doses of 20 μg MERS-CoV mRNA vaccine did not have any detectable replicating MERS-CoV virus in their lungs.

FIG. **21** is a graph showing the MERS-CoV neutralizing antibody titers in New Zealand white rabbits immunized with MERS-CoV mRNA vaccine encoding the full-length Spike protein. Immunization of the in New Zealand white rabbits were carried out as described in FIGS. **21**A-**21**C. The results show that two doses of 20 μg MERS-CoV mRNA vaccine induced a significant amount of neutralizing antibodies against MERS-CoV (EC_{50} between 500-1000). The MERS-CoV mRNA vaccine induced antibody titer is 3-5 fold better than any other vaccines tested in the same model.

DETAILED DESCRIPTION

The present disclosure provides, in some embodiments, vaccines that comprise RNA (e.g., mRNA) polynucleotides encoding a human metapneumovirus (hMPV) antigenic polypeptide, a parainfluenza virus type 3 (PIV3) antigenic polypeptide, a respiratory syncytial virus (RSV) antigenic polypeptide, a measles virus (MeV) antigenic polypeptide, or a betacoronavirus antigenic polypeptide (e.g., Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV, human coronavirus (HCoV)-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH (New Haven) and HCoV-HKU1) (see, e.g., Esper F. et al. *Emerging Infectious Diseases,* 12(5), 2006; and Pyrc K. et al. *Journal of Virology,* 81(7):3051-57, 2007, the contents of each of which is here incorporated by reference in their entirety). The present disclosure also provides, in some embodiments, combination vaccines that comprise at least one RNA (e.g., mRNA) polynucleotide encoding at least two antigenic polypeptides selected from hMPV antigenic polypeptides, PIV3 antigenic polypeptides, RSV antigenic polypeptides, MeV antigenic polypeptides and BetaCoV antigenic polypeptides. Also provided herein are methods of administering the RNA (e.g., mRNA) vaccines, methods of producing the RNA (e.g., mRNA) vaccines, compositions (e.g., pharmaceutical compositions) comprising the RNA (e.g., mRNA) vaccines, and nucleic acids (e.g., DNA) encoding the RNA (e.g., mRNA) vaccines. In some embodiments, a RNA (e.g., mRNA) vaccine comprises an adjuvant, such as a flagellin adjuvant, as provided herein.

The RNA (e.g., mRNA) vaccines (e.g., hMPV, PIV3, RSV, MeV, BetaCoV RNA vaccines and combinations thereof), in some embodiments, may be used to induce a balanced immune response, comprising both cellular and humoral immunity, without many of the risks associated with DNA vaccination.

The entire contents of International Application No. PCT/US2015/02740 is incorporated herein by reference.

Human Metapneumovirus (hMPV)

hMPV shares substantial homology with respiratory syncytial virus (RSV) in its surface glycoproteins. hMPV fusion protein (F) is related to other paramyxovirus fusion proteins and appears to have homologous regions that may have similar functions. The hMPV fusion protein amino acid sequence contains features characteristic of other paramyxovirus F proteins, including a putative cleavage site and potential N-linked glycosylation sites. Paramyxovirus fusion proteins are synthesized as inactive precursors (F0) that are cleaved by host cell proteases into the biologically fusion-active F1 and F2 domains (see, e.g., Cseke G. et al. *Journal of Virology* 2007; 81(2):698-707, incorporated herein by reference). hMPV has one putative cleavage site, in contrast to the two sites established for RSV F, and only shares 34% amino acid sequence identity with RSV F. F2 is extracellular and disulfide linked to F1. Fusion proteins are type I glycoproteins existing as trimers, with two 4-3 heptad repeat domains at the N- and C-terminal regions of the protein (HR1 and HR2), which form coiled-coil alpha-helices. These coiled coils become apposed in an antiparallel fashion when the protein undergoes a conformational change into the fusogenic state. There is a hydrophobic fusion peptide N proximal to the N-terminal heptad repeat, which is thought to insert into the target cell membrane, while the association of the heptad repeats brings the transmembrane domain into close proximity, inducing membrane fusion (see, e.g., Baker, K A et al. *Mol. Cell* 1999; 3:309-319). This mechanism has been proposed for a number of different viruses, including RSV, influenza virus, and human immunodeficiency virus. Fusion proteins are major antigenic determinants for all known paramyxoviruses and for other viruses that possess similar fusion proteins such as human immunodeficiency virus, influenza virus, and Ebola virus.

In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding hMPV fusion protein (F). In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding a F1 or F2 subunit of a hMPV F protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding hMPV glycoprotein (G). In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding hMPV matrix protein (M). In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding hMPV phosphoprotein (P). In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding hMPV nucleoprotein (N). In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding hMPV SH protein (SH).

In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein, M protein, P protein, N protein and SH protein.

In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and G protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and M protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and P protein.

In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and N protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and SH protein.

In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein and M protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein and P protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein and N protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein and SH protein.

In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and M protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and P protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and N protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and SH protein.

A hMPV vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one hMPV antigenic polypeptide identified by any one of SEQ ID NO: 5-8 (Table 3; see also amino acid sequences of Table 4).

A hMPV vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide encoded by a nucleic acid (e.g., DNA) identified by any one of SEQ ID NO: 1-4 (Table 2).

The present disclosure is not limited by a particular strain of hMPV. The strain of hMPV used in a vaccine may be any strain of hMPV. Non-limiting examples of strains of hMPV for use as provide herein include the CAN98-75 (CAN75) and the CAN97-83 (CAN83) hMPV strains (Skiadopoulos M H et al. *J Virol.* 20014; 78(13)6927-37, incorporated herein by reference), a hMPV A1, A2, B1 or B2 strain (see, e.g., de Graaf M et al. *The Journal of General Virology* 2008; 89:975-83; Peret T C T et al. *The Journal of Infectious Disease* 2002; 185:1660-63, incorporated herein by reference), a hMPV isolate TN/92-4 (e.g., SEQ ID NO: 1 and 5), a hMPV isolate NL/1/99 (e.g., SEQ ID NO: 2 and 6), or a hMPV isolate PER/CFI0497/2010/B (e.g., SEQ ID NO: 3 and 7).

In some embodiments, at least one hMPV antigenic polypeptide is obtained from a hMPV A1, A2, B1 or B2 strain (see, e.g., de Graaf M et al. *The Journal of General Virology* 2008; 89:975-83; Peret T C T et al. *The Journal of Infectious Disease* 2002; 185:1660-63, incorporated herein by reference). In some embodiments, at least one antigenic polypeptide is obtained from the CAN98-75 (CAN75) hMPV strain. In some embodiments, at least one antigenic polypeptide is obtained from the CAN97-83 (CAN83) hMPV strain. In some embodiments, at least one antigenic polypeptide is obtained from hMPV isolate TN/92-4 (e.g., SEQ ID NO: 1 and 5). In some embodiments, at least one antigenic polypeptide is obtained from hMPV isolate NL/1/99 (e.g., SEQ ID NO: 2 and 6). In some embodiments, at least one antigenic polypeptide is obtained from hMPV isolate PER/CFI0497/2010/B (e.g., SEQ ID NO: 3 and 7).

In some embodiments, hMPV vaccines comprise RNA (e.g., mRNA) polynucleotides encoding a hMPV antigenic polypeptides having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with hMPV F protein and having F protein activity.

A protein is considered to have F protein activity if, for example, the protein acts to fuse the viral envelope and host cell plasma membrane, mediates viral entry into a host cell via an interaction with arginine-glycine-aspartate RGD-binding integrins, or a combination thereof (see, e.g., Cox R G et al. *J Virol.* 2012; 88(22):12148-60, incorporated herein by reference).

In some embodiments, hMPV vaccines comprise RNA (e.g., mRNA) polynucleotides encoding hMPV antigenic polypeptides having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with hMPV G protein and having G protein activity.

A protein is considered to have G protein activity if, for example, the protein acts to modulate (e.g., inhibit) hMPV-induced cellular (immune) responses (see, e.g., Bao X et al. *PLoS Pathog.* 2008; 4(5):e1000077, incorporated herein by reference).

Human Parainfluenza Virus Type 3 (PIV3)

Parainfluenza viruses belong to the family Paramyxoviridae. These are enveloped viruses with a negative-sense single-stranded RNA genome. Parainfluenza viruses belong to the subfamily Paramyxoviridae, which is subdivided into three genera: Respirovirus (PIV-1, PIV-3, and Sendai virus (SeV)), Rubulavirus (PIV-2, PIV-4 and mumps virus) and Morbillivirus (measles virus, rinderpest virus and canine distemper virus (CDV)). Their genome, a ~15 500 nucleotide-long negative-sense RNA molecule, encodes two envelope glycoproteins, the hemagglutinin-neuraminidase (HN), the fusion protein (F or F0), which is cleaved into F1 and F2 subunits, a matrix protein (M), a nucleocapsid protein (N) and several nonstructural proteins including the viral replicase (L). All parainfluenza viruses, except for PIV-1, express a non-structural V protein that blocks IFN signaling in the infected cell and acts therefore as a virulence factor (see, e.g., Nishio M et al. *J Virol.* 2008; 82(13):6130-38).

PIV3 hemagglutinin-neuraminidase (HN), a structural protein, is found on the viral envelope, where it is necessary for attachment and cell entry. It recognizes and binds to sialic acid-containing receptors on the host cell's surface. As a neuroaminidase, HN removes sialic acid from virus particles, preventing self-aggregation of the virus, and promoting the efficient spread of the virus. Furthermore, HN promotes the activity of the fusion (F or F0) protein, contributing to the penetration of the host cell's surface.

PIV3 fusion protein (PIV3 F) is located on the viral envelope, where it facilitates the viral fusion and cell entry. The F protein is initially inactive, but proteolytic cleavage leads to its active forms, F1 and F2, which are linked by disulfide bonds. This occurs when the HN protein binds its

receptor on the host cell's surface. During early phases of infection, the F glycoprotein mediates penetration of the host cell by fusion of the viral envelope to the plasma membrane. In later stages of the infection, the F protein facilitates the fusion of the infected cells with neighboring uninfected cells, which leads to the formation of a syncytium and spread of the infection.

PIV3 matrix protein (M) is found within the viral envelope and assists with viral assembly. It interacts with the nucleocapsid and envelope glycoproteins, where it facilitates the budding of progeny viruses through its interactions with specific sites on the cytoplasmic tail of the viral glycoproteins and nucleocapsid. It also plays a role in transporting viral components to the budding site.

PIV3 phosphoprotein (P) and PIV3 large polymerase protein (L) are found in the nucleocapsid where they form part of the RNA polymerase complex. The L protein, a viral RNA-dependent RNA polymerase, facilitates genomic transcription, while the host cell's ribosomes translate the viral mRNA into viral proteins.

PIV3 V is a non-structural protein that blocks IFN signaling in the infected cell, therefore acting as a virulence factor.

PIV3 nucleoprotein (N) encapsidates the genome in a ratio of 1 N per 6 ribonucleotides, protecting it from nucleases. The nucleocapsid (NC) has a helical structure.

The encapsidated genomic RNA is termed the NC and serves as template for transcription and replication. During replication, encapsidation by PIV3 N is coupled to RNA synthesis and all replicative products are resistant to nucleases. PIV3 N homo-multimerizes to form the nucleocapsid and binds to viral genomic RNA. PIV3 N binds the P protein and thereby positions the polymerase on the template.

In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding PIV3 fusion protein (F). In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding a F1 or F2 subunit of a PIV3 F protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding PIV3 hemagglutinin-neuraminidase (HN) (see, e.g., van Wyke Coelingh K L et al. *J Virol.* 1987; 61(5):1473-77, incorporated herein by reference). In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding PIV3 matrix protein (M). In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding PIV3 phosphoprotein (P). In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding PIV3 nucleoprotein (N).

In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, HN protein, M protein, P protein, and N protein.

In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and HN protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and M protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and P protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and N protein.

In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HN protein and M protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HN protein and P protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HN protein and N protein.

In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, HN protein and M protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, HN protein and P protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, HN protein and N protein.

A PIV3 vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one PIV3 antigenic polypeptide identified by any one of SEQ ID NO: 12-13 (Table 6; see also amino acid sequences of Table 7).

A PIV3 vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide encoded by a nucleic acid (e.g., DNA) identified by any one of SEQ ID NO: 9-12 (Table 5; see also nucleic acid sequences of Table 7).

The present disclosure is not limited by a particular strain of PIV3. The strain of PIV3 used in a vaccine may be any strain of PIV3. A non-limiting example of a strain of PIV3 for use as provide herein includes HPIV3/*Homo sapiens*/PER/FLA4815/2008.

In some embodiments, PIV3 vaccines comprise RNA (e.g., mRNA) polynucleotides encoding a PIV3 antigenic polypeptides having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with PIV3 F protein and having F protein activity.

In some embodiments, PIV3 vaccines comprise RNA (e.g., mRNA) polynucleotides encoding PIV3 antigenic polypeptides having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with PIV3 hemagglutinin-neuraminidase (HN) and having hemagglutinin-neuraminidase activity.

A protein is considered to have hemagglutinin-neuraminidase activity if, for example, it is capable of both receptor binding and receptor cleaving. Such proteins are major surface glycoproteins that have functional sites for cell attachment and for neuraminidase activity. They are able to cause red blood cells to agglutinate and to cleave the glycosidic linkages of neuraminic acids, so they have the potential to both bind a potential host cell and then release the cell if necessary, for example, to prevent self-aggregation of the virus.

In some embodiments, PIV3 vaccines comprise RNA (e.g., mRNA) polynucleotides encoding PIV3 antigenic polypeptides having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with PIV3 HN, F (e.g., F, F1 or F2), M, N, L or V and having HN, F (e.g., F, F1 or F2), M, N, L or V activity, respectively.

Respiratory Syncytial Virus (RSV)

RSV is a negative-sense, single-stranded RNA virus of the genus Pneumovirinae. The virus is present in at least two antigenic subgroups, known as Group A and Group B, primarily resulting from differences in the surface G glycoproteins. Two RSV surface glycoproteins—G and F—mediate attachment with and attachment to cells of the respiratory epithelium. F surface glycoproteins mediate coalescence of neighboring cells. This results in the forma-

tion of syncytial cells. RSV is the most common cause of bronchiolitis. Most infected adults develop mild cold-like symptoms such as congestion, low-grade fever, and wheezing. Infants and small children may suffer more severe symptoms such as bronchiolitis and pneumonia. The disease may be transmitted among humans via contact with respiratory secretions.

The genome of RSV encodes at least three surface glycoproteins, including F, G, and SH, four nucleocapsid proteins, including L, P, N, and M2, and one matrix protein, M. Glycoprotein F directs viral penetration by fusion between the virion and the host membrane. Glycoprotein G is a type II transmembrane glycoprotein and is the major attachment protein. SH is a short integral membrane protein. Matrix protein M is found in the inner layer of the lipid bilayer and assists virion formation. Nucleocapsid proteins L, P, N, and M2 modulate replication and transcription of the RSV genome. It is thought that glycoprotein G tethers and stabilizes the virus particle at the surface of bronchial epithelial cells, while glycoprotein F interacts with cellular glycosaminoglycans to mediate fusion and delivery of the RSV virion contents into the host cell (Krzyzaniak M A et al. *PLoS Pathog* 2013; 9(4)).

In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding L protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding P protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding N protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding M2 protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding M protein.

In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein, L protein, P protein, N protein, M2 protein and M protein.

In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and G protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and L protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and P protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and N protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and M2 protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and M protein.

In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein and L protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein and P protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein and N protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein and M2 protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein and M protein.

In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and L protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and P protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and N protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and M2 protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and M protein.

The present disclosure is not limited by a particular strain of RSV. The strain of RSV used in a vaccine may be any strain of RSV.

In some embodiments, RSV vaccines comprise RNA (e.g., mRNA) polynucleotides encoding a RSV antigenic polypeptides having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with RSV F protein and having F protein activity.

In some embodiments, RSV vaccines comprise RNA (e.g., mRNA) polynucleotides encoding RSV antigenic polypeptides having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with RSV G protein and having G protein activity.

A protein is considered to have G protein activity if, for example, the protein acts to modulate (e.g., inhibit) hMPV-induced cellular (immune) responses (see, e.g., Bao X et al. *PLoS Pathog.* 2008; 4(5):e1000077, incorporated herein by reference).

Measles Virus (MeV) Molecular epidemiologic investigations and virologic surveillance contribute notably to the control and prevention of measles. Nearly half of measles-related deaths worldwide occur in India, yet virologic surveillance data are incomplete for many regions of the country. Previous studies have documented the presence of measles virus genotypes D4, D7, and D8 in India, and genotypes D5, D9, D11, H1, and G3 have been detected in neighboring countries. Recently, MeV genotype B3 was detected in India (Kuttiatt V S et al. *Emerg Infect Dis.* 2014; 20(10): 1764-66).

The glycoprotein complex of paramyxoviruses mediates receptor binding and membrane fusion. In particular, the MeV fusion (F) protein executes membrane fusion, after receptor binding by the hemagglutinin (HA) protein (Muhlebach M D et al. *Journal of Virology* 2008; 82(22):11437-45). The MeV P gene codes for three proteins: P, an essential polymerase cofactor, and V and C, which have multiple functions but are not strictly required for viral propagation in cultured cells. V shares the amino-terminal domain with P but has a zinc-binding carboxyl-terminal domain, whereas C is translated from an overlapping reading frame. The MeV C protein is an infectivity factor. During replication, the P protein binds incoming monomeric nucleocapsid (N) proteins with its amino-terminal domain and positions them for assembly into the nascent ribonucleocapsid. The P protein amino-terminal domain is natively unfolded (Deveaux P et al. *Journal of Virology* 2004; 78(21): 11632-40).

In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding P protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding V protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding C protein.

In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein, F protein, P protein, V protein and C protein.

In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein and F protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein and P protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein and V protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein and C protein.

some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and P protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and V protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and C protein.

In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein, F protein and P protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein, F protein and V protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein, F protein and C protein.

In some embodiments, MeV vaccines comprise RNA (e.g., mRNA) encoding a MeV antigenic polypeptide having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with MeV HA protein and having MeV HA protein activity.

In some embodiments, MeV vaccines comprise RNA (e.g., mRNA) encoding a MeV antigenic polypeptide having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with MeV F protein and having MeV F protein activity.

A protein is considered to have HA protein activity if the protein mediates receptor binding and/or membrane fusion. MeV F protein executes membrane fusion, after receptor binding by the MeV HA protein.

A MeV vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one MeV antigenic polypeptide identified by any one of SEQ ID NO: 47-50 (Table 14; see also amino acid sequences of Table 15).

A MeV vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide identified by any one of SEQ ID NO: 37, 40, 43, 46 (Table 13).

A MeV vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide encoded by a nucleic acid (e.g., DNA) identified by any one of SEQ ID NO: 35, 36, 38, 39, 41, 42, 44 and 45 (Table 13).

The present disclosure is not limited by a particular strain of MeV. The strain of MeV used in a vaccine may be any strain of MeV. Non-limiting examples of strains of MeV for use as provide herein include B3/B3.1, C2, D4, D6, D7, D8, G3, H1, Moraten, Rubeovax, MVi/New Jersey.USA/45.05, MVi/Texas.USA/4.07, AIK-C, MVi/New York.USA/26.09/3, MVi/California.USA/16.03, MVi/Virginia.USA/15.09, MVi/California.USA/8.04, and MVi/Pennsylvania.USA/20.09.

MeV proteins may be from MeV genotype D4, D5, D7, D8, D9, D11, H1, G3 or B3. In some embodiments, a MeV HA protein or a MeV F protein is from MeV genotype D8. In some embodiments, a MeV HA protein or a MeV F protein is from MeV genotype B3.

Betacoronaviruses (BetaCoV)

MERS-CoV. MERS-CoV is a positive-sense, single-stranded RNA virus of the genus Betacoronavirus. The genomes are phylogenetically classified into two clades, clade A and clade B. It has a strong tropism for non-ciliated bronchial epithelial cells, evades the innate immune response and antagonizes interferon (IFN) production in infected cells. Dipeptyl peptidase 4 (DDP4, also known as CD26) has been identified as a functional cellular receptor for MERS-CoV. Its enzymatic activity is not required for infection, although its amino acid sequence is highly conserved across species and is expressed in the human bronchial epithelium and kidneys. Most infected individuals develop severe acute respiratory illnesses, including fever, cough, and shortness of breath, and the virus can be fatal. The disease may be transmitted among humans, generally among those in close contact.

The genome of MERS-CoV encodes at least four unique accessory proteins, such as 3, 4a, 4b and 5, two replicase proteins (open reading frame 1a and 1b), and four major structural proteins, including spike (S), envelope (E), nucleocapsid (N), and membrane (M) proteins (Almazan F et al. *MBio* 2013; 4(5):e00650-13). The accessory proteins play nonessential roles in MERS-CoV replication, but they are likely structural proteins or interferon antagonists, modulating in vivo replication efficiency and/or pathogenesis, as in the case of SARS-CoV (Almazan F et al. *MBio* 2013; 4(5):e00650-13; Totura A L et al. *Curr Opin Virol* 2012; 2(3):264-75; Scobey T et al. *Proc Natl Acad Sci USA* 2013; 110(40):16157-62). The other proteins of MERS-CoV maintain different functions in virus replication. The E protein, for example, involves in virulence, and deleting the E-coding gene results in replication-competent and propagation-defective viruses or attenuated viruses (Almazan F et al. *MBio* 2013; 4(5):e00650-13). The S protein is particularly essential in mediating virus binding to cells expressing receptor dipeptidyl peptidase-4 (DPP4) through receptor-binding domain (RBD) in the S1 subunit, whereas the S2 subunit subsequently mediates virus entry via fusion of the virus and target cell membranes (Li F. *J Virol* 2015; 89(4): 1954-64; Raj V S et al. *Nature* 2013; 495(7440):251-4).

In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding the S1 subunit of the S protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding the S2 subunit of the S

protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding E protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding N protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding M protein.

In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2), E protein, N protein and M protein.

In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2) and E protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2) and N protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2) and M protein.

In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2), E protein and M protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2), E protein and N protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2), M protein and N protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding E protein, M protein and N protein.

A MERS-CoV vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one MERS-CoV antigenic polypeptide identified by any one of SEQ ID NO: 24-38 or 33 (Table 11; see also amino acid sequences of Table 12).

A MERS-CoV vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide encoded by a nucleic acid (e.g., DNA) identified by any one of SEQ ID NO: 20-23 (Table 10).

The present disclosure is not limited by a particular strain of MERS-CoV. The strain of MERS-CoV used in a vaccine may be any strain of MERS-CoV. Non-limiting examples of strains of MERS-CoV for use as provide herein include Riyadh_14_2013, and 2cEMC/2012, Hasa_1_2013.

SARS-CoV. The genome of SARS-CoV includes of a single, positive-strand RNA that is approximately 29,700 nucleotides long. The overall genome organization of SARS-CoV is similar to that of other coronaviruses. The reference genome includes 13 genes, which encode at least 14 proteins. Two large overlapping reading frames (ORFs) encompass 71% of the genome. The remainder has 12 potential ORFs, including genes for structural proteins S (spike), E (small envelope), M (membrane), and N (nucleocapsid). Other potential ORFs code for unique putative SARS-CoV-specific polypeptides that lack obvious sequence similarity to known proteins. A detailed analysis of the SARS-CoV genome has been published in *J Mol Biol* 2003; 331: 991-1004.

In some embodiments, a SARS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2), E protein, N protein and M protein.

In some embodiments, a SARS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2) and E protein. In some embodiments, a SARS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2) and N protein. In some embodiments, a SARS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2) and M protein.

In some embodiments, a SARS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2), E protein and M protein. In some embodiments, a SARS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2), E protein and N protein. In some embodiments, a SARS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2), M protein and N protein. In some embodiments, a SARS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding E protein, M protein and N protein.

A SARS-CoV vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one SARS-CoV antigenic polypeptide identified by any one of SEQ ID NO: 29, 32 or 34 (Table 11; see also amino acid sequences of Table 12).

The present disclosure is not limited by a particular strain of SARS-CoV. The strain of SARS-CoV used in a vaccine may be any strain of SARS-CoV.

HCoV-OC43.

Human coronavirus OC43 is an enveloped, positive-sense, single-stranded RNA virus in the species Betacoronavirus-1 (genus Betacoronavirus, subfamily Coronavirinae, family Coronaviridae, order Nidovirales). Four HCoV-OC43 genotypes (A to D), have been identified with genotype D most likely arising from recombination. The complete genome sequencing of two genotype C and D strains and bootscan analysis shows recombination events between genotypes B and C in the generation of genotype D. Of 29 strains identified, none belong to the more ancient genotype A. Along with HCoV-229E, a species in the Alphacoronavirus genus, HCoV-OC43 are among the known viruses that cause the common cold. Both viruses can cause severe lower respiratory tract infections, including pneumonia in infants, the elderly, and immunocompromised individuals such as those undergoing chemotherapy and those with HIV-AIDS.

HCoV-HKU1.

Human coronavirus HKU1 (HCoV-H KU 1) is a positive-sense, single-stranded RNA virus with the HE gene, which distinguishes it as a group 2, or betacoronavirus. It was discovered in January 2005 in two patients in Hong Kong. The genome of HCoV-HKU1 is a 29,926-nucleotide, polyadenylated RNA. The GC content is 32%, the lowest among all known coronaviruses. The genome organization is the same as that of other group II coronaviruses, with the characteristic gene order 1a, 1b, HE, S, E, M, and N. Furthermore, accessory protein genes are present between the S and E genes (ORF4) and at the position of the N gene (ORF8). The TRS is presumably located within the AAUCUAAAC sequence, which precedes each ORF except E. As in sialodacryoadenitis virus and mouse hepatitis virus (MHV), translation of the E protein possibly occurs via an internal ribosomal entry site. The 3' untranslated region contains a predicted stem-loop structure immediately down-

stream of the N ORF (nucleotide position 29647 to 29711). Further downstream, a pseudoknot structure is present at nucleotide position 29708 to 29760. Both RNA structures are conserved in group II coronaviruses and are critical for virus replication.

HCoV-NL63.

The RNA genome of human coronavirus NL63 (HCoV-NL63) is 27,553 nucleotides, with a poly(A) tail (FIG. **1**). With a GC content of 34%, HCoV-NL63 has one of the lowest GC contents of the coronaviruses, for which GC content ranges from 32 to 42%. Untranslated regions of 286 and 287 nucleotides are present at the 5' and 3' termini, respectively. Genes predicted to encode the S, E, M, and N proteins are found in the 3' part of the HCoV-NL63 genome. The HE gene, which is present in some group II coronaviruses, is absent, and there is only a single, monocistronic accessory protein ORF (ORF3) located between the S and E genes. Subgenomic mRNAs are generated for all ORFs (S, ORF3, E, M, and N), and the core sequence of the TRS of HCoV-NL63 is defined as AACUAAA. This sequence is situated upstream of every ORF except for the E ORF, which contains the suboptimal core sequence AACUAUA. Interestingly, a 13-nucleotide sequence with perfect homology to the leader sequence is situated upstream of the suboptimal E TRS. Annealing of this 13-nucleotide sequence to the leader sequence may act as a compensatory mechanism for the disturbed leader-TRS/body-TRS interaction.

HCoV-229E.

Human coronavirus 229E (HCoV-229E) is a single-stranded, positive-sense, RNA virus species in the Alphacoronavirus genus of the subfamily Coronavirinae, in the family Coronaviridae, of the order Nidovirales. Along with Human coronavirus OC43, it is responsible for the common cold. HCoV-NL63 and HCoV-229E are two of the four human coronaviruses that circulate worldwide. These two viruses are unique in their relationship towards each other. Phylogenetically, the viruses are more closely related to each other than to any other human coronavirus, yet they only share 65% sequence identity. Moreover, the viruses use different receptors to enter their target cell. HCoV-NL63 is associated with croup in children, whereas all signs suggest that the virus probably causes the common cold in healthy adults. HCoV-229E is a proven common cold virus in healthy adults, so it is probable that both viruses induce comparable symptoms in adults, even though their mode of infection differs (HCoV-NL63 and HCoV-229E are two of the four human coronaviruses that circulate worldwide. These two viruses are unique in their relationship towards each other. Phylogenetically, the viruses are more closely related to each other than to any other human coronavirus, yet they only share 65% sequence identity. Moreover, the viruses use different receptors to enter their target cell. HCoV-NL63 is associated with croup in children, whereas all signs suggest that the virus probably causes the common cold in healthy adults. HCoV-229E is a proven common cold virus in healthy adults, so it is probable that both viruses induce comparable symptoms in adults, even though their mode of infection differs (Dijkman R. et al. *J Formos Med Assoc.* 2009 April; 108(4):270-9, the contents of which is incorporated herein by reference in their entirety).

Combination Vaccines

Embodiments of the present disclosure also provide combination RNA (e.g., mRNA) vaccines. A "combination RNA (e.g., mRNA) vaccine" of the present disclosure refers to a vaccine comprising at least one (e.g., at least 2, 3, 4, or 5) RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a combination of any two or more (or all of) antigenic polypeptides selected from hMPV antigenic polypeptides, PIV3 antigenic polypeptides, RSV antigenic polypeptides, MeV antigenic polypeptides, and BetaCoV antigenic polypeptides (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a PIV3 antigenic polypeptide, a RSV antigenic polypeptide, a MeV antigenic polypeptide, and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide and a PIV3 antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide and a RSV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide and a MeV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide and a BetaCoV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a PIV3 antigenic polypeptide and a RSV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a PIV3 antigenic polypeptide and a MeV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a PIV3 antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a RSV antigenic polypeptide and a MeV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a RSV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a MeV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a PIV3 antigenic polypeptide, a RSV antigenic polypeptide and a MeV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide

encoding a hMPV antigenic polypeptide, a PIV3 antigenic polypeptide, a RSV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a PIV3 antigenic polypeptide, a MeV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a RSV antigenic polypeptide, a MeV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a PIV3 antigenic polypeptide, a RSV antigenic polypeptide, a MeV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

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In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a PIV3 antigenic polypeptide and a MeV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a PIV3 antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a RSV antigenic polypeptide and a MeV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a RSV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a MeV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a PIV3 antigenic polypeptide, a RSV antigenic polypeptide and a MeV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a PIV3 antigenic polypeptide, a RSV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a RSV antigenic polypeptide, a MeV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

Other combination respiratory virus RNA (e.g., mRNA) vaccines are encompassed by the present disclosure.

It has been discovered that the mRNA vaccines described herein are superior to current vaccines in several ways. First, the lipid nanoparticle (LNP) delivery is superior to other formulations including a protamine base approach described in the literature and no additional adjuvants are to be necessary. The use of LNPs enables the effective delivery of chemically modified or unmodified mRNA vaccines. Additionally it has been demonstrated herein that both modified and unmodified LNP formulated mRNA vaccines were superior to conventional vaccines by a significant degree. In some embodiments the mRNA vaccines of the invention are superior to conventional vaccines by a factor of at least 10 fold, 20 fold, 40 fold, 50 fold, 100 fold, 500 fold or 1,000 fold.

Although attempts have been made to produce functional RNA vaccines, including mRNA vaccines and self-replicating RNA vaccines, the therapeutic efficacy of these RNA vaccines have not yet been fully established. Quite surprisingly, the inventors have discovered, according to aspects of the invention a class of formulations for delivering mRNA vaccines in vivo that results in significantly enhanced, and in many respects synergistic, immune responses including enhanced antigen generation and functional antibody production with neutralization capability. These results can be achieved even when significantly lower doses of the mRNA are administered in comparison with mRNA doses used in other classes of lipid based formulations. The formulations of the invention have demonstrated significant unexpected in vivo immune responses sufficient to establish the efficacy of functional mRNA vaccines as prophylactic and therapeutic agents. Additionally, self-replicating RNA vaccines rely on viral replication pathways to deliver enough RNA to a cell to produce an immunogenic response. The formulations of the invention do not require viral replication to produce enough protein to result in a strong immune response. Thus, the mRNA of the invention are not self-replicating RNA and do not include components necessary for viral replication.

The invention involves, in some aspects, the surprising finding that lipid nanoparticle (LNP) formulations significantly enhance the effectiveness of mRNA vaccines, including chemically modified and unmodified mRNA vaccines. The efficacy of mRNA vaccines formulated in LNP was examined in vivo using several distinct antigens. The results presented herein demonstrate the unexpected superior efficacy of the mRNA vaccines formulated in LNP over other commercially available vaccines.

In addition to providing an enhanced immune response, the formulations of the invention generate a more rapid immune response with fewer doses of antigen than other vaccines tested. The mRNA-LNP formulations of the invention also produce quantitatively and qualitatively better immune responses than vaccines formulated in a different carriers.

The data described herein demonstrate that the formulations of the invention produced significant unexpected

improvements over existing antigen vaccines. Additionally, the mRNA-LNP formulations of the invention are superior to other vaccines even when the dose of mRNA is lower than other vaccines. Mice immunized with either 10 μg or 2 μg doses of an hMPV fusion protein mRNA LNP vaccine or a PIV3 mRNA LNP vaccine produced neutralizing antibodies which for instance, successfully neutralized the hMPV B2 virus. A 10 μg dose of mRNA vaccine protected 100% of mice from lethal challenge and drastically reduced the viral titer after challenge (~2 log reduction).

Two 20 μg doses of MERS-CoV mRNA LNP vaccine significantly reduced viral load and induced significant amount of neutralizing antibodies against MERS-CoV (ECso between 500-1000). The MERS-CoV mRNA vaccine induced antibody titer was 3-5 fold better than any other vaccines tested in the same model.

The LNP used in the studies described herein has been used previously to deliver siRNA in various animal models as well as in humans. In view of the observations made in association with the siRNA delivery of LNP formulations, the fact that LNP is useful in vaccines is quite surprising. It has been observed that therapeutic delivery of siRNA formulated in LNP causes an undesirable inflammatory response associated with a transient IgM response, typically leading to a reduction in antigen production and a compromised immune response. In contrast to the findings observed with siRNA, the LNP-mRNA formulations of the invention are demonstrated herein to generate enhanced IgG levels, sufficient for prophylactic and therapeutic methods rather than transient IgM responses.

Nucleic Acids/Polynucleotides

Respiratory virus vaccines, as provided herein, comprise at least one (one or more) ribonucleic acid (RNA) (e.g., mRNA) polynucleotide having an open reading frame encoding at least one antigenic polypeptide selected from hMPV, PIV3, RSV, MeV and BetaCoV (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1) antigenic polypeptides. The term "nucleic acid" includes any compound and/or substance that comprises a polymer of nucleotides (nucleotide monomer). These polymers are referred to as polynucleotides. Thus, the terms "nucleic acid" and "polynucleotide" are used interchangeably.

Nucleic acids may be or may include, for example, ribonucleic acids (RNAs), deoxyribonucleic acids (DNAs), threose nucleic acids (TNAs), glycol nucleic acids (GNAs), peptide nucleic acids (PNAs), locked nucleic acids (LNAs, including LNA having a β-D-ribo configuration, α-LNA having an α-L-ribo configuration (a diastereomer of LNA), 2'-amino-LNA having a 2'-amino functionalization, and 2'-amino-α-LNA having a 2'-amino functionalization), ethylene nucleic acids (ENA), cyclohexenyl nucleic acids (CeNA) or chimeras or combinations thereof.

In some embodiments, polynucleotides of the present disclosure function as messenger RNA (mRNA). "Messenger RNA" (mRNA) refers to any polynucleotide that encodes a (at least one) polypeptide (a naturally-occurring, non-naturally-occurring, or modified polymer of amino acids) and can be translated to produce the encoded polypeptide in vitro, in vivo, in situ or ex vivo. The skilled artisan will appreciate that, except where otherwise noted, polynucleotide sequences set forth in the instant application will recite "T"s in a representative DNA sequence but where the sequence represents RNA (e.g., mRNA), the "T"s would be substituted for "U"s. Thus, any of the RNA polynucleotides encoded by a DNA identified by a particular sequence identification number may also comprise the corresponding RNA (e.g., mRNA) sequence encoded by the DNA, where each "T" of the DNA sequence is substituted with "U."

The basic components of an mRNA molecule typically include at least one coding region, a 5' untranslated region (UTR), a 3' UTR, a 5' cap and a poly-A tail. Polynucleotides of the present disclosure may function as mRNA but can be distinguished from wild-type mRNA in their functional and/or structural design features, which serve to overcome existing problems of effective polypeptide expression using nucleic-acid based therapeutics.

In some embodiments, a RNA polynucleotide of an RNA (e.g., mRNA) vaccine encodes 2-10, 2-9, 2-8, 2-7, 2-6, 2-5, 2-4, 2-3, 3-10, 3-9, 3-8, 3-7, 3-6, 3-5, 3-4, 4-10, 4-9, 4-8, 4-7, 4-6, 4-5, 5-10, 5-9, 5-8, 5-7, 5-6, 6-10, 6-9, 6-8, 6-7, 7-10, 7-9, 7-8, 8-10, 8-9 or 9-10 antigenic polypeptides. In some embodiments, a RNA (e.g., mRNA) polynucleotide of a respiratory virus vaccine encodes at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 antigenic polypeptides. In some embodiments, a RNA (e.g., mRNA) polynucleotide of a respiratory virus vaccine encodes at least 100 or at least 200 antigenic polypeptides. In some embodiments, a RNA polynucleotide of an respiratory virus vaccine encodes 1-10, 5-15, 10-20, 15-25, 20-30, 25-35, 30-40, 35-45, 40-50, 1-50, 1-100, 2-50 or 2-100 antigenic polypeptides.

Polynucleotides of the present disclosure, in some embodiments, are codon optimized. Codon optimization methods are known in the art and may be used as provided herein. Codon optimization, in some embodiments, may be used to match codon frequencies in target and host organisms to ensure proper folding; bias GC content to increase mRNA stability or reduce secondary structures; minimize tandem repeat codons or base runs that may impair gene construction or expression; customize transcriptional and translational control regions; insert or remove protein trafficking sequences; remove/add post translation modification sites in encoded protein (e.g. glycosylation sites); add, remove or shuffle protein domains; insert or delete restriction sites; modify ribosome binding sites and mRNA degradation sites; adjust translational rates to allow the various domains of the protein to fold properly; or to reduce or eliminate problem secondary structures within the polynucleotide. Codon optimization tools, algorithms and services are known in the art—non-limiting examples include services from GeneArt (Life Technologies), DNA2.0 (Menlo Park Calif.) and/or proprietary methods. In some embodiments, the open reading frame (ORF) sequence is optimized using optimization algorithms.

In some embodiments, a codon optimized sequence shares less than 95% sequence identity, less than 90% sequence identity, less than 85% sequence identity, less than 80% sequence identity, or less than 75% sequence identity to a naturally-occurring or wild-type sequence (e.g., a naturally-occurring or wild-type mRNA sequence encoding a polypeptide or protein of interest (e.g., an antigenic protein or antigenic polypeptide)).

In some embodiments, a codon-optimized sequence shares between 65% and 85% (e.g., between about 67% and about 85%, or between about 67% and about 80%) sequence identity to a naturally-occurring sequence or a wild-type sequence (e.g., a naturally-occurring or wild-type mRNA sequence encoding a polypeptide or protein of interest (e.g., an antigenic protein or polypeptide)). In some embodiments, a codon-optimized sequence shares between 65% and 75%, or about 80% sequence identity to a naturally-occurring sequence or wild-type sequence (e.g., a naturally-occurring

or wild-type mRNA sequence encoding a polypeptide or protein of interest (e.g., an antigenic protein or polypeptide)).

In some embodiments a codon-optimized RNA (e.g., mRNA) may, for instance, be one in which the levels of G/C are enhanced. The G/C-content of nucleic acid molecules may influence the stability of the RNA. RNA having an increased amount of guanine (G) and/or cytosine (C) residues may be functionally more stable than nucleic acids containing a large amount of adenine (A) and thymine (T) or uracil (U) nucleotides. WO02/098443 discloses a pharmaceutical composition containing an mRNA stabilized by sequence modifications in the translated region. Due to the degeneracy of the genetic code, the modifications work by substituting existing codons for those that promote greater RNA stability without changing the resulting amino acid. The approach is limited to coding regions of the RNA.

Antigens/Antigenic Polypeptides

In some embodiments, an antigenic polypeptide (e.g., a hMPV, PIV3, RSV, MeV or BetaCoV antigenic polypeptide) is longer than 25 amino acids and shorter than 50 amino acids. Polypeptides include gene products, naturally occurring polypeptides, synthetic polypeptides, homologs, orthologs, paralogs, fragments and other equivalents, variants, and analogs of the foregoing. A polypeptide may be a single molecule or may be a multi-molecular complex such as a dimer, trimer or tetramer. Polypeptides may also comprise single chain polypeptides or multichain polypeptides, such as antibodies or insulin, and may be associated or linked to each other. Most commonly, disulfide linkages are found in multichain polypeptides. The term "polypeptide" may also apply to amino acid polymers in which at least one amino acid residue is an artificial chemical analogue of a corresponding naturally-occurring amino acid.

A "polypeptide variant" is a molecule that differs in its amino acid sequence relative to a native sequence or a reference sequence. Amino acid sequence variants may possess substitutions, deletions, insertions, or a combination of any two or three of the foregoing, at certain positions within the amino acid sequence, as compared to a native sequence or a reference sequence. Ordinarily, variants possess at least 50% identity to a native sequence or a reference sequence. In some embodiments, variants share at least 80% identity or at least 90% identity with a native sequence or a reference sequence.

In some embodiments "variant mimics" are provided. A "variant mimic" contains at least one amino acid that would mimic an activated sequence. For example, glutamate may serve as a mimic for phosphoro-threonine and/or phosphoro-serine. Alternatively, variant mimics may result in deactivation or in an inactivated product containing the mimic. For example, phenylalanine may act as an inactivating substitution for tyrosine, or alanine may act as an inactivating substitution for serine.

"Orthologs" refers to genes in different species that evolved from a common ancestral gene by speciation. Normally, orthologs retain the same function in the course of evolution. Identification of orthologs is important for reliable prediction of gene function in newly sequenced genomes.

"Analogs" is meant to include polypeptide variants that differ by one or more amino acid alterations, for example, substitutions, additions or deletions of amino acid residues that still maintain one or more of the properties of the parent or starting polypeptide.

The present disclosure provides several types of compositions that are polynucleotide or polypeptide based, including variants and derivatives. These include, for example, substitutional, insertional, deletion and covalent variants and derivatives. The term "derivative" is synonymous with the term "variant" and generally refers to a molecule that has been modified and/or changed in any way relative to a reference molecule or a starting molecule.

As such, polynucleotides encoding peptides or polypeptides containing substitutions, insertions and/or additions, deletions and covalent modifications with respect to reference sequences, in particular the polypeptide sequences disclosed herein, are included within the scope of this disclosure. For example, sequence tags or amino acids, such as one or more lysines, can be added to peptide sequences (e.g., at the N-terminal or C-terminal ends). Sequence tags can be used for peptide detection, purification or localization. Lysines can be used to increase peptide solubility or to allow for biotinylation. Alternatively, amino acid residues located at the carboxy and amino terminal regions of the amino acid sequence of a peptide or protein may optionally be deleted providing for truncated sequences. Certain amino acids (e.g., C-terminal residues or N-terminal residues) alternatively may be deleted depending on the use of the sequence, as for example, expression of the sequence as part of a larger sequence that is soluble, or linked to a solid support.

"Substitutional variants" when referring to polypeptides are those that have at least one amino acid residue in a native or starting sequence removed and a different amino acid inserted in its place at the same position. Substitutions may be single, where only one amino acid in the molecule has been substituted, or they may be multiple, where two or more (e.g., 3, 4 or 5) amino acids have been substituted in the same molecule.

As used herein the term "conservative amino acid substitution" refers to the substitution of an amino acid that is normally present in the sequence with a different amino acid of similar size, charge, or polarity. Examples of conservative substitutions include the substitution of a non-polar (hydrophobic) residue such as isoleucine, valine and leucine for another non-polar residue. Likewise, examples of conservative substitutions include the substitution of one polar (hydrophilic) residue for another such as between arginine and lysine, between glutamine and asparagine, and between glycine and serine. Additionally, the substitution of a basic residue such as lysine, arginine or histidine for another, or the substitution of one acidic residue such as aspartic acid or glutamic acid for another acidic residue are additional examples of conservative substitutions. Examples of non-conservative substitutions include the substitution of a non-polar (hydrophobic) amino acid residue such as isoleucine, valine, leucine, alanine, methionine for a polar (hydrophilic) residue such as cysteine, glutamine, glutamic acid or lysine and/or a polar residue for a non-polar residue.

"Features" when referring to polypeptide or polynucleotide are defined as distinct amino acid sequence-based or nucleotide-based components of a molecule respectively. Features of the polypeptides encoded by the polynucleotides include surface manifestations, local conformational shape, folds, loops, half-loops, domains, half-domains, sites, termini and any combination(s) thereof.

As used herein when referring to polypeptides the term "domain" refers to a motif of a polypeptide having one or more identifiable structural or functional characteristics or properties (e.g., binding capacity, serving as a site for protein-protein interactions).

As used herein when referring to polypeptides the terms "site" as it pertains to amino acid based embodiments is used

synonymously with "amino acid residue" and "amino acid side chain." As used herein when referring to polynucleotides the terms "site" as it pertains to nucleotide based embodiments is used synonymously with "nucleotide." A site represents a position within a peptide or polypeptide or polynucleotide that may be modified, manipulated, altered, derivatized or varied within the polypeptide-based or polynucleotide-based molecules.

As used herein the terms "termini" or "terminus" when referring to polypeptides or polynucleotides refers to an extremity of a polypeptide or polynucleotide respectively. Such extremity is not limited only to the first or final site of the polypeptide or polynucleotide but may include additional amino acids or nucleotides in the terminal regions. Polypeptide-based molecules may be characterized as having both an N-terminus (terminated by an amino acid with a free amino group (NH2)) and a C-terminus (terminated by an amino acid with a free carboxyl group (COOH)). Proteins are in some cases made up of multiple polypeptide chains brought together by disulfide bonds or by non-covalent forces (multimers, oligomers). These proteins have multiple N- and C-termini. Alternatively, the termini of the polypeptides may be modified such that they begin or end, as the case may be, with a non-polypeptide based moiety such as an organic conjugate.

As recognized by those skilled in the art, protein fragments, functional protein domains, and homologous proteins are also considered to be within the scope of polypeptides of interest. For example, provided herein is any protein fragment (meaning a polypeptide sequence at least one amino acid residue shorter than a reference polypeptide sequence but otherwise identical) of a reference protein having a length of 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or longer than 100 amino acids. In another example, any protein that includes a stretch of 20, 30, 40, 50, or 100 (contiguous) amino acids that are 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% identical to any of the sequences described herein can be utilized in accordance with the disclosure. In some embodiments, a polypeptide includes 2, 3, 4, 5, 6, 7, 8, 9, 10, or more mutations as shown in any of the sequences provided herein or referenced herein. In another example, any protein that includes a stretch of 20, 30, 40, 50, or 100 amino acids that are greater than 80%, 90%, 95%, or 100% identical to any of the sequences described herein, wherein the protein has a stretch of 5, 10, 15, 20, 25, or 30 amino acids that are less than 80%, 75%, 70%, 65% to 60% identical to any of the sequences described herein can be utilized in accordance with the disclosure.

Polypeptide or polynucleotide molecules of the present disclosure may share a certain degree of sequence similarity or identity with the reference molecules (e.g., reference polypeptides or reference polynucleotides), for example, with art-described molecules (e.g., engineered or designed molecules or wild-type molecules). The term "identity," as known in the art, refers to a relationship between the sequences of two or more polypeptides or polynucleotides, as determined by comparing the sequences. In the art, identity also means the degree of sequence relatedness between two sequences as determined by the number of matches between strings of two or more amino acid residues or nucleic acid residues. Identity measures the percent of identical matches between the smaller of two or more sequences with gap alignments (if any) addressed by a particular mathematical model or computer program (e.g., "algorithms"). Identity of related peptides can be readily calculated by known methods. "% identity" as it applies to polypeptide or polynucleotide sequences is defined as the percentage of residues (amino acid residues or nucleic acid residues) in the candidate amino acid or nucleic acid sequence that are identical with the residues in the amino acid sequence or nucleic acid sequence of a second sequence after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent identity. Methods and computer programs for the alignment are well known in the art. Identity depends on a calculation of percent identity but may differ in value due to gaps and penalties introduced in the calculation. Generally, variants of a particular polynucleotide or polypeptide have at least 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% but less than 100% sequence identity to that particular reference polynucleotide or polypeptide as determined by sequence alignment programs and parameters described herein and known to those skilled in the art. Such tools for alignment include those of the BLAST suite (Stephen F. Altschul, et al. (1997)." Gapped BLAST and PSI-BLAST: a new generation of protein database search programs," *Nucleic Acids Res.* 25:3389-3402). Another popular local alignment technique is based on the Smith-Waterman algorithm (Smith, T. F. & Waterman, M. S. (1981) "Identification of common molecular subsequences." *J. Mol. Biol.* 147:195-197). A general global alignment technique based on dynamic programming is the Needleman-Wunsch algorithm (Needleman, S. B. & Wunsch, C. D. (1970) "A general method applicable to the search for similarities in the amino acid sequences of two proteins." *J. Mol. Biol.* 48:443-453). More recently, a Fast Optimal Global Sequence Alignment Algorithm (FOGSAA) was developed that purportedly produces global alignment of nucleotide and protein sequences faster than other optimal global alignment methods, including the Needleman-Wunsch algorithm. Other tools are described herein, specifically in the definition of "identity" below.

As used herein, the term "homology" refers to the overall relatedness between polymeric molecules, e.g. between nucleic acid molecules (e.g. DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Polymeric molecules (e.g. nucleic acid molecules (e.g. DNA molecules and/or RNA molecules) and/or polypeptide molecules) that share a threshold level of similarity or identity determined by alignment of matching residues are termed homologous. Homology is a qualitative term that describes a relationship between molecules and can be based upon the quantitative similarity or identity. Similarity or identity is a quantitative term that defines the degree of sequence match between two compared sequences. In some embodiments, polymeric molecules are considered to be "homologous" to one another if their sequences are at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical or similar. The term "homologous" necessarily refers to a comparison between at least two sequences (polynucleotide or polypeptide sequences). Two polynucleotide sequences are considered homologous if the polypeptides they encode are at least 50%, 60%, 70%, 80%, 90%, 95%, or even 99% for at least one stretch of at least 20 amino acids. In some embodiments, homologous polynucleotide sequences are characterized by the ability to encode a stretch of at least 4-5 uniquely specified amino acids. For polynucleotide sequences less than 60 nucleotides in length, homology is determined by the ability to encode a stretch of at least 4-5 uniquely specified amino acids. Two protein sequences are considered homologous if the proteins are at least 50%, 60%, 70%, 80%, or 90% identical for at least one stretch of at least 20 amino acids.

Homology implies that the compared sequences diverged in evolution from a common origin. The term "homolog" refers to a first amino acid sequence or nucleic acid sequence (e.g., gene (DNA or RNA) or protein sequence) that is related to a second amino acid sequence or nucleic acid sequence by descent from a common ancestral sequence. The term "homolog" may apply to the relationship between genes and/or proteins separated by the event of speciation or to the relationship between genes and/or proteins separated by the event of genetic duplication. "Orthologs" are genes (or proteins) in different species that evolved from a common ancestral gene (or protein) by speciation. Typically, orthologs retain the same function in the course of evolution. "Paralogs" are genes (or proteins) related by duplication within a genome. Orthologs retain the same function in the course of evolution, whereas paralogs evolve new functions, even if these are related to the original one.

The term "identity" refers to the overall relatedness between polymeric molecules, for example, between polynucleotide molecules (e.g. DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of the percent identity of two polynucleic acid sequences, for example, can be performed by aligning the two sequences for optimal comparison purposes (e.g., gaps can be introduced in one or both of a first and a second nucleic acid sequences for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or 100% of the length of the reference sequence. The nucleotides at corresponding nucleotide positions are then compared. When a position in the first sequence is occupied by the same nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which needs to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. For example, the percent identity between two nucleic acid sequences can be determined using methods such as those described in Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; Computer Analysis of Sequence Data, Part I, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; each of which is incorporated herein by reference. For example, the percent identity between two nucleic acid sequences can be determined using the algorithm of Meyers and Miller (CABIOS, 1989, 4:11-17), which has been incorporated into the ALIGN program (version 2.0) using a PAM 120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. The percent identity between two nucleic acid sequences can, alternatively, be determined using the GAP program in the GCG software package using an NWSgapdna.CMP matrix. Methods commonly employed to determine percent identity between sequences include, but are not limited to those disclosed in Carillo, H., and Lipman, D., SIAM *J Applied Math.,* 48:1073 (1988); incorporated herein by reference. Techniques for determining identity are codified in publicly available computer programs. Exemplary computer software to determine homology between two sequences include, but are not limited to, GCG program package, Devereux, J., et al., *Nucleic Acids Research,* 12(1), 387 (1984)), BLASTP, BLASTN, and FASTA Altschul, S. F. et al., *J. Molec. Biol.,* 215, 403 (1990)).

Multiprotein and Multicomponent Vaccines

The present disclosure encompasses respiratory virus vaccines comprising multiple RNA (e.g., mRNA) polynucleotides, each encoding a single antigenic polypeptide, as well as respiratory virus vaccines comprising a single RNA polynucleotide encoding more than one antigenic polypeptide (e.g., as a fusion polypeptide). Thus, a vaccine composition comprising a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a first antigenic polypeptide and a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a second antigenic polypeptide encompasses (a) vaccines that comprise a first RNA polynucleotide encoding a first antigenic polypeptide and a second RNA polynucleotide encoding a second antigenic polypeptide, and (b) vaccines that comprise a single RNA polynucleotide encoding a first and second antigenic polypeptide (e.g., as a fusion polypeptide). RNA (e.g., mRNA) vaccines of the present disclosure, in some embodiments, comprise 2-10 (e.g., 2, 3, 4, 5, 6, 7, 8, 9 or 10), or more, RNA polynucleotides having an open reading frame, each of which encodes a different antigenic polypeptide (or a single RNA polynucleotide encoding 2-10, or more, different antigenic polypeptides). The antigenic polypeptides may be selected from hMPV, PIV3, RSV, MEV and BetaCoV (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1) antigenic polypeptides.

In some embodiments, a respiratory virus vaccine comprises a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a viral capsid protein, a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a viral premembrane/membrane protein, and a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a viral envelope protein. In some embodiments, a respiratory virus vaccine comprises a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a viral fusion (F) protein and a RNA polynucleotide having an open reading frame encoding a viral major surface glycoprotein (G protein). In some embodiments, a vaccine comprises a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a viral F protein. In some embodiments, a vaccine comprises a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a viral G protein. In some embodiments, a vaccine comprises a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a HN protein.

In some embodiments, a multicomponent vaccine comprises at least one RNA (e.g., mRNA) polynucleotide encoding at least one antigenic polypeptide fused to a signal peptide (e.g., any one of SEQ ID NO: 15-19). The signal peptide may be fused at the N-terminus or the C-terminus of an antigenic polypeptide. An antigenic polypeptide fused to a signal peptide may be selected from hMPV, PIV3, RSV, MEV and BetaCoV (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1) antigenic polypeptides.

Signal Peptides

In some embodiments, antigenic polypeptides encoded by respiratory virus RNA (e.g., mRNA) polynucleotides comprise a signal peptide. Signal peptides, comprising the

N-terminal 15-60 amino acids of proteins, are typically needed for the translocation across the membrane on the secretory pathway and, thus, universally control the entry of most proteins both in eukaryotes and prokaryotes to the secretory pathway. Signal peptides generally include three regions: an N-terminal region of differing length, which usually comprises positively charged amino acids; a hydrophobic region; and a short carboxy-terminal peptide region. In eukaryotes, the signal peptide of a nascent precursor protein (pre-protein) directs the ribosome to the rough endoplasmic reticulum (ER) membrane and initiates the transport of the growing peptide chain across it for processing. ER processing produces mature proteins, wherein the signal peptide is cleaved from precursor proteins, typically by a ER-resident signal peptidase of the host cell, or they remain uncleaved and function as a membrane anchor. A signal peptide may also facilitate the targeting of the protein to the cell membrane. The signal peptide, however, is not responsible for the final destination of the mature protein. Secretory proteins devoid of additional address tags in their sequence are by default secreted to the external environment. During recent years, a more advanced view of signal peptides has evolved, showing that the functions and immunodominance of certain signal peptides are much more versatile than previously anticipated.

Respiratory virus vaccines of the present disclosure may comprise, for example, RNA (e.g., mRNA) polynucleotides encoding an artificial signal peptide, wherein the signal peptide coding sequence is operably linked to and is in frame with the coding sequence of the antigenic polypeptide. Thus, respiratory virus vaccines of the present disclosure, in some embodiments, produce an antigenic polypeptide comprising an antigenic polypeptide (e.g., hMPV, PIV3, RSV, MeV or BetaCoV) fused to a signal peptide. In some embodiments, a signal peptide is fused to the N-terminus of the antigenic polypeptide. In some embodiments, a signal peptide is fused to the C-terminus of the antigenic polypeptide.

In some embodiments, the signal peptide fused to the antigenic polypeptide is an artificial signal peptide. In some embodiments, an artificial signal peptide fused to the antigenic polypeptide encoded by the RNA (e.g., mRNA) vaccine is obtained from an immunoglobulin protein, e.g., an IgE signal peptide or an IgG signal peptide. In some embodiments, a signal peptide fused to the antigenic polypeptide encoded by a RNA (e.g., mRNA) vaccine is an Ig heavy chain epsilon-1 signal peptide (IgE HC SP) having the sequence of: MDWTWILFLVAAATRVHS (SEQ ID NO: 16). In some embodiments, a signal peptide fused to the antigenic polypeptide encoded by the (e.g., mRNA) RNA (e.g., mRNA) vaccine is an IgGk chain V-III region HAH signal peptide (IgGk SP) having the sequence of METPAQLLFLLLLWLPDTTG (SEQ ID NO: 15). In some embodiments, the signal peptide is selected from: Japanese encephalitis PRM signal sequence (MLGSNSGQRVVFTILLLLVAPAYS; SEQ ID NO: 17), VSVg protein signal sequence (MKCLLYLAFLFIGVNCA; SEQ ID NO: 18) and Japanese encephalitis JEV signal sequence (MWLVSLAIVTACAGA; SEQ ID NO: 19).

In some embodiments, the antigenic polypeptide encoded by a RNA (e.g., mRNA) vaccine comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, 47-50 or 54-56 (Tables 3, 6, 11, 14 or 17; see also amino acid sequences of Tables 4, 7, 12 or 15) fused to a signal peptide identified by any one of SEQ ID NO: 15-19 (Table 8). The examples disclosed herein are not meant to be limiting and any signal peptide that is known in the art to facilitate targeting of a protein to ER for processing and/or targeting of a protein to the cell membrane may be used in accordance with the present disclosure.

A signal peptide may have a length of 15-60 amino acids. For example, a signal peptide may have a length of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, or 60 amino acids. In some embodiments, a signal peptide has a length of 20-60, 25-60, 30-60, 35-60, 40-60, 45-60, 50-60, 55-60, 15-55, 20-55, 25-55, 30-55, 35-55, 40-55, 45-55, 50-55, 15-50, 20-50, 25-50, 30-50, 35-50, 40-50, 45-50, 15-45, 20-45, 25-45, 30-45, 35-45, 40-45, 15-40, 20-40, 25-40, 30-40, 35-40, 15-35, 20-35, 25-35, 30-35, 15-30, 20-30, 25-30, 15-25, 20-25, or 15-20 amino acids.

A signal peptide is typically cleaved from the nascent polypeptide at the cleavage junction during ER processing. The mature antigenic polypeptide produce by a respiratory virus RNA (e.g., mRNA) vaccine of the present disclosure typically does not comprise a signal peptide.

Chemical Modifications

Respiratory virus vaccines of the present disclosure, in some embodiments, comprise at least RNA (e.g. mRNA) polynucleotide having an open reading frame encoding at least one antigenic polypeptide that comprises at least one chemical modification.

The terms "chemical modification" and "chemically modified" refer to modification with respect to adenosine (A), guanosine (G), uridine (U), thymidine (T) or cytidine (C) ribonucleosides or deoxyribnucleosides in at least one of their position, pattern, percent or population. Generally, these terms do not refer to the ribonucleotide modifications in naturally occurring 5'-terminal mRNA cap moieties. With respect to a polypeptide, the term "modification" refers to a modification relative to the canonical set 20 amino acids. Polypeptides, as provided herein, are also considered "modified" of they contain amino acid substitutions, insertions or a combination of substitutions and insertions.

Polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides), in some embodiments, comprise various (more than one) different modifications. In some embodiments, a particular region of a polynucleotide contains one, two or more (optionally different) nucleoside or nucleotide modifications. In some embodiments, a modified RNA polynucleotide (e.g., a modified mRNA polynucleotide), introduced to a cell or organism, exhibits reduced degradation in the cell or organism, respectively, relative to an unmodified polynucleotide. In some embodiments, a modified RNA polynucleotide (e.g., a modified mRNA polynucleotide), introduced into a cell or organism, may exhibit reduced immunogenicity in the cell or organism, respectively (e.g., a reduced innate response).

Modifications of polynucleotides include, without limitation, those described herein. Polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) may comprise modifications that are naturally-occurring, non-naturally-occurring or the polynucleotide may comprise a combination of naturally-occurring and non-naturally-occurring modifications. Polynucleotides may include any useful modification, for example, of a sugar, a nucleobase, or an internucleoside linkage (e.g., to a linking phosphate, to a phosphodiester linkage or to the phosphodiester backbone).

Polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides), in some embodiments, comprise non-natural modified nucleotides that are introduced during synthesis or post-synthesis of the polynucleotides to achieve desired functions or properties. The modifications may be present on an internucleotide linkages, purine or pyrimidine

bases, or sugars. The modification may be introduced with chemical synthesis or with a polymerase enzyme at the terminal of a chain or anywhere else in the chain. Any of the regions of a polynucleotide may be chemically modified.

The present disclosure provides for modified nucleosides and nucleotides of a polynucleotide (e.g., RNA polynucleotides, such as mRNA polynucleotides). A "nucleoside" refers to a compound containing a sugar molecule (e.g., a pentose or ribose) or a derivative thereof in combination with an organic base (e.g., a purine or pyrimidine) or a derivative thereof (also referred to herein as "nucleobase"). A nucleotide" refers to a nucleoside, including a phosphate group. Modified nucleotides may by synthesized by any useful method, such as, for example, chemically, enzymatically, or recombinantly, to include one or more modified or non-natural nucleosides. Polynucleotides may comprise a region or regions of linked nucleosides. Such regions may have variable backbone linkages. The linkages may be standard phosphdioester linkages, in which case the polynucleotides would comprise regions of nucleotides.

Modified nucleotide base pairing encompasses not only the standard adenosine-thymine, adenosine-uracil, or guanosine-cytosine base pairs, but also base pairs formed between nucleotides and/or modified nucleotides comprising non-standard or modified bases, wherein the arrangement of hydrogen bond donors and hydrogen bond acceptors permits hydrogen bonding between a non-standard base and a standard base or between two complementary non-standard base structures. One example of such non-standard base pairing is the base pairing between the modified nucleotide inosine and adenine, cytosine or uracil. Any combination of base/sugar or linker may be incorporated into polynucleotides of the present disclosure.

Modifications of polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) that are useful in the vaccines of the present disclosure include, but are not limited to the following: 2-methylthio-N6-(cis-hydroxyisopentenyl)adenosine; 2-methylthio-N6-methyladenosine; 2-methylthio-N6-threonyl carbamoyladenosine; N6-glycinylcarbamoyladenosine; N6-isopentenyladenosine; N6-methyladenosine; N6-threonylcarbamoyladenosine; 1,2'-O-dimethyladenosine; 1-methyladenosine; 2'-O-methyladenosine; 2'-O-ribosyladenosine (phosphate); 2-methyladenosine; 2-methylthio-N6 isopentenyladenosine; 2-methylthio-N6-hydroxynorvalyl carbamoyladenosine; 2'-O-methyladenosine; 2'-O-ribosyladenosine (phosphate); Isopentenyladenosine; N6-(cis-hydroxyisopentenyl)adenosine; N6,2'-O-dimethyladenosine; N6,2'-O-dimethyladenosine; N6,N6,2'-O-trimethyladenosine; N6,N6-dimethyladenosine; N6-acetyladenosine; N6-hydroxynorvalylcarbamoyladenosine; N6-methyl-N6-threonylcarbamoyladenosine; 2-methyladenosine; 2-methylthio-N6-isopentenyladenosine; 7-deaza-adenosine; N1-methyl-adenosine; N6, N6 (dimethyl)adenine; N6-cis-hydroxy-isopentenyl-adenosine; α-thio-adenosine; 2 (amino)adenine; 2 (aminopropyl)adenine; 2 (methylthio) N6 (isopentenyl)adenine; 2-(alkyl)adenine; 2-(aminoalkyl)adenine; 2-(aminopropyl)adenine; 2-(halo)adenine; 2-(halo) adenine; 2-(propyl)adenine; 2'-Amino-2'-deoxy-ATP; 2'-Azido-2'-deoxy-ATP; 2'-Deoxy-2'-a-aminoadenosine TP; 2'-Deoxy-2'-a-azidoadenosine TP; 6 (alkyl)adenine; 6 (methyl)adenine; 6-(alkyl)adenine; 6-(methyl)adenine; 7 (deaza)adenine; 8 (alkenyl)adenine; 8 (alkynyl)adenine; 8 (amino)adenine; 8 (thioalkyl)adenine; 8-(alkenyl)adenine; 8-(alkyl)adenine; 8-(alkynyl)adenine; 8-(amino)adenine; 8-(halo)adenine; 8-(hydroxyl)adenine; 8-(thioalkyl)adenine; 8-(thiol)adenine; 8-azido-adenosine; aza adenine; deaza adenine; N6 (methyl)adenine; N6-(isopentyl)adenine; 7-deaza-8-aza-adenosine; 7-methyladenine; 1-Deazaadenosine TP; 2'Fluoro-N6-Bz-deoxyadenosine TP; 2'-OMe-2-Amino-ATP; 2'O-methyl-N6-Bz-deoxyadenosine TP; 2'-a-Ethynyladenosine TP; 2-aminoadenine; 2-Aminoadenosine TP; 2-Amino-ATP; 2'-a-Trifluoromethyladenosine TP; 2-Azidoadenosine TP; 2'-b-Ethynyladenosine TP; 2-Bromoadenosine TP; 2'-b-Trifluoromethyladenosine TP; 2-Chloroadenosine TP; 2'-Deoxy-2', 2'-difluoroadenosine TP; 2'-Deoxy-2'-a-mercaptoadenosine TP; 2'-Deoxy-2'-a-thiomethoxyadenosine TP; 2'-Deoxy-2'-b-aminoadenosine TP; 2'-Deoxy-2'-b-azidoadenosine TP; 2'-Deoxy-2'-b-bromoadenosine TP; 2'-Deoxy-2'-b-chloroadenosine TP; 2'-Deoxy-2'-b-fluoroadenosine TP; 2'-Deoxy-2'-b-iodoadenosine TP; 2'-Deoxy-2'-b-mercaptoadenosine TP; 2'-Deoxy-2'-b-thiomethoxyadenosine TP; 2-Fluoroadenosine TP; 2-Iodoadenosine TP; 2-Mercaptoadenosine TP; 2-methoxy-adenine; 2-methylthio-adenine; 2-Trifluoromethyladenosine TP; 3-Deaza-3-bromoadenosine TP; 3-Deaza-3-chloroadenosine TP; 3-Deaza-3-fluoroadenosine TP; 3-Deaza-3-iodoadenosine TP; 3-Deazaadenosine TP; 4'-Azidoadenosine TP; 4'-Carbocyclic adenosine TP; 4'-Ethynyladenosine TP; 5'-Homo-adenosine TP; 8-Aza-ATP; 8-bromo-adenosine TP; 8-Trifluoromethyladenosine TP; 9-Deazaadenosine TP; 2-aminopurine; 7-deaza-2,6-diaminopurine; 7-deaza-8-aza-2,6-diaminopurine; 7-deaza-8-aza-2-aminopurine; 2,6-diaminopurine; 7-deaza-8-aza-adenine, 7-deaza-2-aminopurine; 2-thiocytidine; 3-methylcytidine; 5-formylcytidine; 5-hydroxymethylcytidine; 5-methylcytidine; N4-acetylcytidine; 2'-O-methylcytidine; 2'-O-methylcytidine; 5,2'-O-dimethylcytidine; 5-formyl-2'-O-methylcytidine; Lysidine; N4,2'-O-dimethylcytidine; N4-acetyl-2'-O-methylcytidine; N4-methylcytidine; N4,N4-Dimethyl-2'-OMe-Cytidine TP; 4-methylcytidine; 5-aza-cytidine; Pseudo-iso-cytidine; pyrrolo-cytidine; α-thio-cytidine; 2-(thio)cytosine; 2'-Amino-2'-deoxy-CTP; 2'-Azido-2'-deoxy-CTP; 2'-Deoxy-2'-a-aminocytidine TP; 2'-Deoxy-2'-a-azidocytidine TP; 3 (deaza) 5 (aza)cytosine; 3 (methyl)cytosine; 3-(alkyl)cytosine; 3-(deaza) 5 (aza)cytosine; 3-(methyl)cytidine; 4,2'-O-dimethylcytidine; 5 (halo)cytosine; 5 (methyl)cytosine; 5 (propynyl)cytosine; 5 (trifluoromethyl)cytosine; 5-(alkyl) cytosine; 5-(alkynyl)cytosine; 5-(halo)cytosine; 5-(propynyl)cytosine; 5-(trifluoromethyl)cytosine; 5-bromo-cytidine; 5-iodo-cytidine; 5-propynyl cytosine; 6-(azo)cytosine; 6-aza-cytidine; aza cytosine; deaza cytosine; N4 (acetyl) cytosine; 1-methyl-1-deaza-pseudoisocytidine; 1-methyl-pseudoisocytidine; 2-methoxy-5-methyl-cytidine; 2-methoxy-cytidine; 2-thio-5-methyl-cytidine; 4-methoxy-1-methyl-pseudoisocytidine; 4-methoxy-pseudoisocytidine; 4-thio-1-methyl-1-deaza-pseudoisocytidine; 4-thio-1-methyl-pseudoisocytidine; 4-thio-pseudoisocytidine; 5-aza-zebularine; 5-methyl-zebularine; pyrrolo-pseudoisocytidine; Zebularine; (E)-5-(2-Bromo-vinyl)cytidine TP; 2,2'-anhydro-cytidine TP hydrochloride; 2'Fluor-N4-Bz-cytidine TP; 2'Fluoro-N4-Acetyl-cytidine TP; 2'-O-Methyl-N4-Acetyl-cytidine TP; 2'O-methyl-N4-Bz-cytidine TP; 2'-a-Ethynylcytidine TP; 2'-a-Trifluoromethylcytidine TP; 2'-b-Ethynylcytidine TP; 2'-b-Trifluoromethylcytidine TP; 2'-Deoxy-2', 2'-difluorocytidine TP; 2'-Deoxy-2'-a-mercaptocytidine TP; 2'-Deoxy-2'-a-thiomethoxycytidine TP; 2'-Deoxy-2'-b-aminocytidine TP; 2'-Deoxy-2'-b-azidocytidine TP; 2'-Deoxy-2'-b-bromocytidine TP; 2'-Deoxy-2'-b-chlorocytidine TP; 2'-Deoxy-2'-b-fluorocytidine TP; 2'-Deoxy-2'-b-iodocytidine TP; 2'-Deoxy-2'-b-mercaptocytidine TP; 2'-Deoxy-2'-b-thiomethoxycytidine TP; 2'-O-Methyl-5-(1-propynyl)cytidine TP; 3'-Ethynylcytidine TP; 4'-Azidocytidine TP; 4'-Carbocyclic cytidine TP; 4'-Ethynylcytidine

TP; 5-(1-Propynyl)ara-cytidine TP; 5-(2-Chloro-phenyl)-2-thiocytidine TP; 5-(4-Amino-phenyl)-2-thiocytidine TP; 5-Aminoallyl-CTP; 5-Cyanocytidine TP; 5-Ethynylara-cytidine TP; 5-Ethynylcytidine TP; 5'-Homo-cytidine TP; 5-Methoxycytidine TP; 5-Trifluoromethyl-Cytidine TP; N4-Amino-cytidine TP; N4-Benzoyl-cytidine TP; Pseudoisocytidine; 7-methylguanosine; N2,2'-O-dimethylguanosine; N2-methylguanosine; Wyosine; 1,2'-O-dimethylguanosine; 1-methylguanosine; 2'-O-methylguanosine; 2'-O-ribosylguanosine (phosphate); 2'-O-methylguanosine; 2'-O-ribosylguanosine (phosphate); 7-aminomethyl-7-deazaguanosine; 7-cyano-7-deazaguanosine; Archaeosine; Methylwyosine; N2,7-dimethylguanosine; N2,N2,2'-O-trimethylguanosine; N2,N2,7-trimethylguanosine; N2,N2-dimethylguanosine; N2,7,2'-O-trimethylguanosine; 6-thio-guanosine; 7-deaza-guanosine; 8-oxo-guanosine; N1-methyl-guanosine; α-thio-guanosine; 2 (propyl)guanine; 2-(alkyl)guanine; 2'-Amino-2'-deoxy-GTP; 2'-Azido-2'-deoxy-GTP; 2'-Deoxy-2'-a-aminoguanosine TP; 2'-Deoxy-2'-a-azidoguanosine TP; 6 (methyl)guanine; 6-(alkyl)guanine; 6-(methyl)guanine; 6-methyl-guanosine; 7 (alkyl)guanine; 7 (deaza)guanine; 7 (methyl)guanine; 7-(alkyl)guanine; 7-(deaza)guanine; 7-(methyl)guanine; 8 (alkyl)guanine; 8 (alkynyl)guanine; 8 (halo)guanine; 8 (thioalkyl)guanine; 8-(alkenyl)guanine; 8-(alkyl)guanine; 8-(alkynyl)guanine; 8-(amino)guanine; 8-(halo)guanine; 8-(hydroxyl)guanine; 8-(thioalkyl)guanine; 8-(thiol)guanine; aza guanine; deaza guanine; N (methyl)guanine; N-(methyl)guanine; 1-methyl-6-thio-guanosine; 6-methoxy-guanosine; 6-thio-7-deaza-8-aza-guanosine; 6-thio-7-deaza-guanosine; 6-thio-7-methyl-guanosine; 7-deaza-8-aza-guanosine; 7-methyl-8-oxo-guanosine; N2,N2-dimethyl-6-thio-guanosine; N2-methyl-6-thio-guanosine; 1-Me-GTP; 2'Fluoro-N2-isobutyl-guanosine TP; 2'O-methyl-N2-isobutyl-guanosine TP; 2'-a-Ethynylguanosine TP; 2'-a-Trifluoromethylguanosine TP; 2'-b-Ethynylguanosine TP; 2'-b-Trifluoromethylguanosine TP; 2'-Deoxy-2', 2'-difluoroguanosine TP; 2'-Deoxy-2'-a-mercaptoguanosine TP; 2'-Deoxy-2'-a-thiomethoxyguanosine TP; 2'-Deoxy-2'-b-aminoguanosine TP; 2'-Deoxy-2'-b-azidoguanosine TP; 2'-Deoxy-2'-b-bromoguanosine TP; 2'-Deoxy-2'-b-chloroguanosine TP; 2'-Deoxy-2'-b-fluoroguanosine TP; 2'-Deoxy-2'-b-iodoguanosine TP; 2'-Deoxy-2'-b-mercaptoguanosine TP; 2'-Deoxy-2'-b-thiomethoxyguanosine TP; 4'-Azidoguanosine TP; 4'-Carbocyclic guanosine TP; 4'-Ethynylguanosine TP; 5'-Homo-guanosine TP; 8-bromo-guanosine TP; 9-Deaza-guanosine TP; N2-isobutyl-guanosine TP; 1-methylinosine; Inosine; 1,2'-O-dimethylinosine; 2'-O-methylinosine; 7-methylinosine; 2'-O-methylinosine; Epoxyqueuosine; galactosyl-queuosine; Mannosylqueuosine; Queuosine; allyamino-thymidine; aza thymidine; deaza thymidine; deoxy-thymidine; 2'-O-methyluridine; 2-thiouridine; 3-methyluridine; 5-carboxymethyluridine; 5-hydroxyuridine; 5-methyluridine; 5-taurinomethyl-2-thiouridine; 5-taurinomethyluridine; Dihydrouridine; Pseudouridine; (3-(3-amino-3-carboxypropyl)uridine; 1-methyl-3-(3-amino-5-carboxypropyl)pseudouridine; 1-methylpseduouridine; 1-methyl-pseudouridine; 2'-O-methyluridine; 2'-O-methylpseudouridine; 2'-O-methyluridine; 2-thio-2'-O-methyluridine; 3-(3-amino-3-carboxypropyl)uridine; 3,2'-O-dimethyluridine; 3-Methyl-pseudo-Uridine TP; 4-thiouridine; 5-(carboxyhydroxymethyl)uridine; 5-(carboxyhydroxymethyl)uridine methyl ester; 5,2'-O-dimethyluridine; 5,6-dihydro-uridine; 5-aminomethyl-2-thiouridine; 5-carbamoylmethyl-2'-O-methyluridine; 5-carbamoylmethyluridine; 5-carboxyhydroxymethyluridine; 5-carboxyhydroxymethyluridine methyl ester; 5-carboxymethylaminomethyl-2'-O-methyluridine; 5-carboxymethylaminomethyl-2-thiouridine; 5-carboxymethylaminomethyl-2-thiouridine; 5-carboxymethylaminomethyluridine; 5-carboxymethylaminomethyluridine; 5-Carbamoylmethyluridine TP; 5-methoxycarbonylmethyl-2'-O-methyluridine; 5-methoxycarbonylmethyl-2-thiouridine; 5-methoxycarbonylmethyluridine; 5-methoxyuridine; 5-methyl-2-thiouridine; 5-methylaminomethyl-2-selenouridine; 5-methylaminomethyl-2-thiouridine; 5-methylaminomethyluridine; 5-Methyldihydrouridine; 5-Oxyacetic acid-Uridine TP; 5-Oxyacetic acid-methyl ester-Uridine TP; N1-methyl-pseudo-uridine; uridine 5-oxyacetic acid; uridine 5-oxyacetic acid methyl ester; 3-(3-Amino-3-carboxypropyl)-Uridine TP; 5-(iso-Pentenylaminomethyl)-2-thiouridine TP; 5-(iso-Pentenylaminomethyl)-2'-O-methyluridine TP; 5-(iso-Pentenylaminomethyl)uridine TP; 5-propynyl uracil; α-thio-uridine; 1 (aminoalkylamino-carbonylethylenyl)-2 (thio)-pseudouracil; 1 (aminoalkylaminocarbonylethylenyl)-2,4-(dithio)pseudouracil; 1 (aminoalkylaminocarbonylethylenyl)-4 (thio)pseudouracil; 1 (aminoalkylaminocarbonylethylenyl)-pseudouracil; 1 (aminocarbonylethylenyl)-2(thio)-pseudouracil; 1 (aminocarbonylethylenyl)-2,4-(dithio)pseudouracil; 1 (aminocarbonylethylenyl)-4 (thio)pseudouracil; 1 (aminocarbonylethylenyl)-pseudouracil; 1 substituted 2(thio)-pseudouracil; 1 substituted 2,4-(dithio)pseudouracil; 1 substituted 4 (thio) pseudouracil; 1 substituted pseudouracil; 1-(aminoalkylamino-carbonylethylenyl)-2-(thio)-pseudouracil; 1-Methyl-3-(3-amino-3-carboxypropyl) pseudouridine TP; 1-Methyl-3-(3-amino-3-carboxypropyl)pseudo-UTP; 1-Methyl-pseudo-UTP; 2 (thio)pseudouracil; 2' deoxy uridine; 2' fluorouridine; 2-(thio)uracil; 2,4-(dithio)psuedouracil; 2' methyl, 2'amino, 2' azido, 2'fluro-guanosine; 2'-Amino-2'-deoxy-UTP; 2'-Azido-2'-deoxy-UTP; 2'-Azido-deoxyuridine TP; 2'-O-methylpseudouridine; 2' deoxy uridine; 2' fluorouridine; 2'-Deoxy-2'-a-aminouridine TP; 2'-Deoxy-2'-a-azidouridine TP; 2-methylpseudouridine; 3 (3 amino-3 carboxypropyl)uracil; 4 (thio)pseudouracil; 4-(thio)pseudouracil; 4-(thio)uracil; 4-thiouracil; 5 (1,3-diazole-1-alkyl)uracil; 5 (2-aminopropyl)uracil; 5 (aminoalkyl)uracil; 5 (dimethylaminoalkyl)uracil; 5 (guanidiniumalkyl)uracil; 5 (methoxycarbonylmethyl)-2-(thio)uracil; 5 (methoxycarbonyl-methyl)uracil; 5 (methyl) 2 (thio)uracil; 5 (methyl) 2,4 (dithio)uracil; 5 (methyl) 4 (thio)uracil; 5 (methylaminomethyl)-2 (thio)uracil; 5 (methylaminomethyl)-2,4 (dithio)uracil; 5 (methylaminomethyl)-4 (thio) uracil; 5 (propynyl)uracil; 5 (trifluoromethyl)uracil; 5-(2-aminopropyl)uracil; 5-(alkyl)-2-(thio)pseudouracil; 5-(alkyl)-2,4 (dithio)pseudouracil; 5-(alkyl)-4 (thio) pseudouracil; 5-(alkyl)pseudouracil; 5-(alkyl)uracil; 5-(alkynyl)uracil; 5-(allylamino)uracil; 5-(cyanoalkyl)uracil; 5-(dialkylaminoalkyl)uracil; 5-(dimethylaminoalkyl) uracil; 5-(guanidiniumalkyl)uracil; 5-(halo)uracil; 5-(1,3-diazole-1-alkyl)uracil; 5-(methoxy)uracil; 5-(methoxycarbonylmethyl)-2-(thio)uracil; 5-(methoxycarbonyl-methyl)uracil; 5-(methyl) 2(thio)uracil; 5-(methyl) 2,4 (dithio)uracil; 5-(methyl) 4 (thio)uracil; 5-(methyl)-2-(thio)pseudouracil; 5-(methyl)-2,4 (dithio)pseudouracil; 5-(methyl)-4 (thio)pseudouracil; 5-(methyl)pseudouracil; 5-(methylaminomethyl)-2 (thio)uracil; 5-(methylaminomethyl)-2,4(dithio)uracil; 5-(methylaminomethyl)-4-(thio) uracil; 5-(propynyl)uracil; 5-(trifluoromethyl)uracil; 5-aminoallyl-uridine; 5-bromo-uridine; 5-iodo-uridine; 5-uracil; 6 (azo)uracil; 6-(azo)uracil; 6-aza-uridine; allyamino-uracil; aza uracil; deaza uracil; N3 (methyl)uracil; Pseudo-UTP-1-2-ethanoic acid; Pseudouracil; 4-Thio-pseudo-UTP; 1-carboxymethyl-pseudouridine; 1-methyl-1-

deaza-pseudouridine; 1-propynyl-uridine; 1-taurinomethyl-1-methyl-uridine; 1-taurinomethyl-4-thio-uridine; 1-taurinomethyl-pseudouridine; 2-methoxy-4-thio-pseudouridine; 2-thio-1-methyl-1-deaza-pseudouridine; 2-thio-1-methyl-pseudouridine; 2-thio-5-aza-uridine; 2-thio-dihydropseudouridine; 2-thio-dihydrouridine; 2-thio-pseudouridine; 4-methoxy-2-thio-pseudouridine; 4-methoxy-pseudouridine; 4-thio-1-methyl-pseudouridine; 4-thio-pseudouridine; 5-aza-uridine; Dihydropseudouridine; (±) 1-(2-Hydroxypropyl)pseudouridine TP; (2R)-1-(2-Hydroxypropyl)pseudouridine TP; (2S)-1-(2-Hydroxypropyl) pseudouridine TP; (E)-5-(2-Bromo-vinyl)ara-uridine TP; (E)-5-(2-Bromo-vinyl)uridine TP; (Z)-5-(2-Bromo-vinyl) ara-uridine TP; (Z)-5-(2-Bromo-vinyl)uridine TP; 1-(2,2,2-Trifluoroethyl)-pseudo-UTP; 1-(2,2,3,3,3-Pentafluoropropyl)pseudouridine TP; 1-(2,2-Diethoxyethyl)pseudouridine TP; 1-(2,4,6-Trimethylbenzyl)pseudouridine TP; 1-(2,4,6-Trimethyl-benzyl)pseudo-UTP; 1-(2,4,6-Trimethyl-phenyl) pseudo-UTP; 1-(2-Amino-2-carboxyethyl)pseudo-UTP; 1-(2-Amino-ethyl)pseudo-UTP; 1-(2-Hydroxyethyl) pseudouridine TP; 1-(2-Methoxyethyl)pseudouridine TP; 1-(3,4-Bis-trifluoromethoxybenzyl)pseudouridine TP; 1-(3,4-Dimethoxybenzyl)pseudouridine TP; 1-(3-Amino-3-carboxypropyl)pseudo-UTP; 1-(3-Amino-propyl)pseudo-UTP; 1-(3-Cyclopropyl-prop-2-ynyl)pseudouridine TP; 1-(4-Amino-4-carboxybutyl)pseudo-UTP; 1-(4-Amino-benzyl) pseudo-UTP; 1-(4-Amino-butyl)pseudo-UTP; 1-(4-Amino-phenyl)pseudo-UTP; 1-(4-Azidobenzyl)pseudouridine TP; 1-(4-Bromobenzyl)pseudouridine TP; 1-(4-Chlorobenzyl) pseudouridine TP; 1-(4-Fluorobenzyl)pseudouridine TP; 1-(4-Iodobenzyl)pseudouridine TP; 1-(4-Methanesulfonyl-benzyl)pseudouridine TP; 1-(4-Methoxybenzyl)pseudouridine TP; 1-(4-Methoxy-benzyl)pseudo-UTP; 1-(4-Methoxy-phenyl)pseudo-UTP; 1-(4-Methylbenzyl)pseudouridine TP; 1-(4-Methyl-benzyl)pseudo-UTP; 1-(4-Nitrobenzyl) pseudouridine TP; 1-(4-Nitro-benzyl)pseudo-UTP; 1(4-Nitro-phenyl)pseudo-UTP; 1-(4-Thiomethoxybenzyl) pseudouridine TP; 1-(4-Trifluoromethoxybenzyl) pseudouridine TP; 1-(4-Trifluoromethylbenzyl) pseudouridine TP; 1-(5-Amino-pentyl)pseudo-UTP; 1-(6-Amino-hexyl)pseudo-UTP; 1,6-Dimethyl-pseudo-UTP; 1-[3-(2-{2-[2-(2-Aminoethoxy)-ethoxy]-ethoxy}-ethoxy)-propionyl]pseudouridine TP; 1-{3-[2-(2-Aminoethoxy)-ethoxy]-propionyl}pseudouridine TP; 1-Acetylpseudouridine TP; 1-Alkyl-6-(1-propynyl)-pseudo-UTP; 1-Alkyl-6-(2-propynyl)-pseudo-UTP; 1-Alkyl-6-allyl-pseudo-UTP; 1-Alkyl-6-ethynyl-pseudo-UTP; 1-Alkyl-6-homoallyl-pseudo-UTP; 1-Alkyl-6-vinyl-pseudo-UTP; 1-Allylpseudouridine TP; 1-Aminomethyl-pseudo-UTP; 1-Benzoylpseudouridine TP; 1-Benzyloxymethylpseudouridine TP; 1-Benzyl-pseudo-UTP; 1-Biotinyl-PEG2-pseudouridine TP; 1-Biotinylpseudouridine TP; 1-Butyl-pseudo-UTP; 1-Cyanomethylpseudouridine TP; 1-Cyclobutylmethyl-pseudo-UTP; 1-Cyclobutyl-pseudo-UTP; 1-Cycloheptylmethyl-pseudo-UTP; 1-Cycloheptyl-pseudo-UTP; 1-Cyclohexylmethyl-pseudo-UTP; 1-Cyclohexyl-pseudo-UTP; 1-Cyclooctylmethyl-pseudo-UTP; 1-Cyclooctyl-pseudo-UTP; 1-Cyclopentylmethyl-pseudo-UTP; 1-Cyclopentyl-pseudo-UTP; 1-Cyclopropylmethyl-pseudo-UTP; 1-Cyclopropyl-pseudo-UTP; 1-Ethyl-pseudo-UTP; 1-Hexyl-pseudo-UTP; 1-Homoallylpseudouridine TP; 1-Hydroxymethylpseudouridine TP; 1-iso-propyl-pseudo-UTP; 1-Me-2-thio-pseudo-UTP; 1-Me-4-thio-pseudo-UTP; 1-Me-alpha-thio-pseudo-UTP; 1-Methanesulfonylmethylpseudouridine TP; 1-Methoxymethylpseudouridine TP; 1-Methyl-6-(2,2,2-Trifluoroethyl)pseudo-UTP; 1-Methyl-6-(4-morpholino)-pseudo-UTP; 1-Methyl-6-(4-thiomorpholino)-pseudo-UTP; 1-Methyl-6-(substituted phenyl) pseudo-UTP; 1-Methyl-6-amino-pseudo-UTP; 1-Methyl-6-azido-pseudo-UTP; 1-Methyl-6-bromo-pseudo-UTP; 1-Methyl-6-butyl-pseudo-UTP; 1-Methyl-6-chloro-pseudo-UTP; 1-Methyl-6-cyano-pseudo-UTP; 1-Methyl-6-dimethylamino-pseudo-UTP; 1-Methyl-6-ethoxy-pseudo-UTP; 1-Methyl-6-ethylcarboxylate-pseudo-UTP; 1-Methyl-6-ethyl-pseudo-UTP; 1-Methyl-6-fluoro-pseudo-UTP; 1-Methyl-6-formyl-pseudo-UTP; 1-Methyl-6-hydroxyamino-pseudo-UTP; 1-Methyl-6-hydroxy-pseudo-UTP; 1-Methyl-6-iodo-pseudo-UTP; 1-Methyl-6-iso-propyl-pseudo-UTP; 1-Methyl-6-methoxy-pseudo-UTP; 1-Methyl-6-methylamino-pseudo-UTP; 1-Methyl-6-phenyl-pseudo-UTP; 1-Methyl-6-propyl-pseudo-UTP; 1-Methyl-6-tert-butyl-pseudo-UTP; 1-Methyl-6-trifluoromethoxy-pseudo-UTP; 1-Methyl-6-trifluoromethyl-pseudo-UTP; 1-Morpholinomethylpseudouridine TP; 1-Pentyl-pseudo-UTP; 1-Phenyl-pseudo-UTP; 1-Pivaloylpseudouridine TP; 1-Propargylpseudouridine TP; 1-Propyl-pseudo-UTP; 1-propynyl-pseudouridine; 1-p-tolyl-pseudo-UTP; 1-tert-Butyl-pseudo-UTP; 1-Thiomethoxymethylpseudouridine TP; 1-Thiomorpholinomethylpseudouridine TP; 1-Trifluoroacetylpseudouridine TP; 1-Trifluoromethyl-pseudo-UTP; 1-Vinylpseudouridine TP; 2,2'-anhydro-uridine TP; 2'-bromo-deoxyuridine TP; 2'-F-5-Methyl-2'-deoxy-UTP; 2'-OMe-5-Me-UTP; 2'-OMe-pseudo-UTP; 2'-a-Ethynyluridine TP; 2'-a-Trifluoromethyluridine TP; 2'-b-Ethynyluridine TP; 2'-b-Trifluoromethyluridine TP; 2'-Deoxy-2', 2'-difluorouridine TP; 2'-Deoxy-2'-a-mercaptouridine TP; 2'-Deoxy-2'-a-thiomethoxyuridine TP; 2'-Deoxy-2'-b-aminouridine TP; 2'-Deoxy-2'-b-azidouridine TP; 2'-Deoxy-2'-b-bromouridine TP; 2'-Deoxy-2'-b-chlorouridine TP; 2'-Deoxy-2'-b-fluorouridine TP; 2'-Deoxy-2'-b-iodouridine TP; 2'-Deoxy-2'-b-mercaptouridine TP; 2'-Deoxy-2'-b-thiomethoxyuridine TP; 2-methoxy-4-thio-uridine; 2-methoxyuridine; 2'-O-Methyl-5-(1-propynyl)uridine TP; 3-Alkyl-pseudo-UTP; 4'-Azidouridine TP; 4'-Carbocyclic uridine TP; 4'-Ethynyluridine TP; 5-(1-Propynyl)ara-uridine TP; 5-(2-Furanyl)uridine TP; 5-Cyanouridine TP; 5-Dimethylaminouridine TP; 5'-Homo-uridine TP; 5-iodo-2'-fluoro-deoxyuridine TP; 5-Phenylethynyluridine TP; 5-Trideuteromethyl-6-deuterouridine TP; 5-Trifluoromethyl-Uridine TP; 5-Vinylarauridine TP; 6-(2,2,2-Trifluoroethyl)-pseudo-UTP; 6-(4-Morpholino)-pseudo-UTP; 6-(4-Thiomorpholino)-pseudo-UTP; 6-(Substituted-Phenyl)-pseudo-UTP; 6-Amino-pseudo-UTP; 6-Azido-pseudo-UTP; 6-Bromo-pseudo-UTP; 6-Butyl-pseudo-UTP; 6-Chloro-pseudo-UTP; 6-Cyano-pseudo-UTP; 6-Dimethylamino-pseudo-UTP; 6-Ethoxy-pseudo-UTP; 6-Ethylcarboxylate-pseudo-UTP; 6-Ethyl-pseudo-UTP; 6-Fluoro-pseudo-UTP; 6-Formyl-pseudo-UTP; 6-Hydroxyamino-pseudo-UTP; 6-Hydroxy-pseudo-UTP; 6-Iodo-pseudo-UTP; 6-iso-Propyl-pseudo-UTP; 6-Methoxy-pseudo-UTP; 6-Methylamino-pseudo-UTP; 6-Methyl-pseudo-UTP; 6-Phenyl-pseudo-UTP; 6-Phenyl-pseudo-UTP; 6-Propyl-pseudo-UTP; 6-tert-Butyl-pseudo-UTP; 6-Trifluoromethoxy-pseudo-UTP; 6-Trifluoromethyl-pseudo-UTP; Alpha-thio-pseudo-UTP; Pseudouridine 1-(4-methylbenzenesulfonic acid) TP; Pseudouridine 1-(4-methylbenzoic acid) TP; Pseudouridine TP 1-[3-(2-ethoxy)]propionic acid; Pseudouridine TP 1-[3-{2-(2-[2-(2-ethoxy)-ethoxy]-ethoxy)-ethoxy}]propionic acid; Pseudouridine TP 1-[3-{2-(2-[2-{2(2-ethoxy)-ethoxy}-ethoxy]-ethoxy)-ethoxy}]propionic acid; Pseudouridine TP 1-[3-{2-(2-[2-ethoxy]-ethoxy)-ethoxy}]propionic acid; Pseudouridine TP 1-[3-{2-(2-ethoxy)-ethoxy}] propionic acid; Pseudouridine TP 1-methylphosphonic acid; Pseudouridine TP 1-methylphosphonic

acid diethyl ester; Pseudo-UTP-N1-3-propionic acid; Pseudo-UTP-N1-4-butanoic acid; Pseudo-UTP-N1-5-pentanoic acid; Pseudo-UTP-N1-6-hexanoic acid; Pseudo-UTP-N1-7-heptanoic acid; Pseudo-UTP-N1-methyl-p-benzoic acid; Pseudo-UTP-N1-p-benzoic acid; Wybutosine; Hydroxywybutosine; Isowyosine; Peroxywybutosine; undermodified hydroxywybutosine; 4-demethylwyosine; 2,6-(diamino)purine; 1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl: 1,3-(diaza)-2-(oxo)-phenthiazin-1-yl; 1,3-(diaza)-2-(oxo)-phenoxazin-1-yl; 1,3,5-(triaza)-2,6-(dioxa)-naphthalene;2 (amino)purine;2,4,5-(trimethyl)phenyl;2' methyl, 2'amino, 2'azido, 2'fluro-cytidine;2' methyl, 2' amino, 2'azido, 2'fluro-adenine;2'methyl, 2'amino, 2' azido, 2'fluro-uridine;2'-amino-2'-deoxyribose; 2-amino-6-Chloro-purine; 2-aza-inosinyl; 2'-azido-2'-deoxyribose; 2'fluoro-2'-deoxyribose; 2'-fluoro-modified bases; 2'-O-methyl-ribose; 2-oxo-7-aminopyridopyrimidin-3-yl; 2-oxo-pyridopyrimidine-3-yl; 2-pyridinone; 3 nitropyrrole; 3-(methyl)-7-(propynyl) isocarbostyrilyl; 3-(methyl)isocarbostyrilyl; 4-(fluoro)-6-(methyl)benzimidazole; 4-(methyl)benzimidazole; 4-(methyl)indolyl; 4,6-(dimethyl)indolyl; 5 nitroindole; 5 substituted pyrimidines; 5-(methyl)isocarbostyrilyl; 5-nitroindole; 6-(aza)pyrimidine; 6-(azo)thymine; 6-(methyl)-7-(aza)indolyl; 6-chloro-purine; 6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; 7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl; 7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl; 7-(aminoalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-1-yl; 7-(aminoalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenthiazin-1-yl; 7-(aminoalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-1-yl; 7-(aza)indolyl; 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazinl-yl; 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl; 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl; 7-(guanidiniumalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-1-yl; 7-(guanidiniumalkyl-hydroxy)-1,3-(diaza)-2-(oxo)-phenthiazin-1-yl; 7-(guanidiniumalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-1-yl; 7-(propynyl)isocarbostyrilyl; 7-(propynyl)isocarbostyrilyl, propynyl-7-(aza)indolyl; 7-deaza-inosinyl; 7-substituted 1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl; 7-substituted 1,3-(diaza)-2-(oxo)-phenoxazin-1-yl; 9-(methyl)-imidizopyridinyl; Aminoindolyl; Anthracenyl; bis-ortho-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; bis-ortho-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; Difluorotolyl; Hypoxanthine; Imidizopyridinyl; Inosinyl; Isocarbostyrilyl; Isoguanisine; N2-substituted purines; N6-methyl-2-amino-purine; N6-substituted purines; N-alkylated derivative; Napthalenyl; Nitrobenzimidazolyl; Nitroimidazolyl; Nitroindazolyl; Nitropyrazolyl; Nubularine; 06-substituted purines; O-alkylated derivative; ortho-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; ortho-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; Oxoformycin TP; para-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; para-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; Pentacenyl; Phenanthracenyl; Phenyl; propynyl-7-(aza)indolyl; Pyrenyl; pyridopyrimidin-3-yl; pyridopyrimidin-3-yl, 2-oxo-7-amino-pyridopyrimidin-3-yl; pyrrolo-pyrimidin-2-on-3-yl; Pyrrolopyrimidinyl; Pyrrolopyrizinyl; Stilbenzyl; substituted 1,2,4-triazoles; Tetracenyl; Tubercidine; Xanthine; Xanthosine-5'-TP; 2-thio-zebularine; 5-aza-2-thio-zebularine; 7-deaza-2-amino-purine; pyridin-4-one ribonucleoside; 2-Amino-riboside-TP; Formycin A TP; Formycin B TP; Pyrrolosine TP; 2'-OH-ara-adenosine TP; 2'-OH-ara-cytidine TP; 2'-OH-ara-uridine TP; 2'-OH-ara-guanosine TP; 5-(2-carbomethoxyvinyl)uridine TP; and N6-(19-Amino-pentaoxanonadecyl)adenosine TP.

In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) include a combination of at least two (e.g., 2, 3, 4 or more) of the aforementioned modified nucleobases.

In some embodiments, modified nucleobases in polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) are selected from the group consisting of pseudouridine (ψ), N1-methylpseudouridine ($m^1\psi$), N1-ethylpseudouridine, 2-thiouridine, 4'-thiouridine, 5-methylcytosine, 2-thio-1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-pseudouridine, 2-thio-5-aza-uridine, 2-thio-dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-pseudouridine, 4-methoxy-2-thio-pseudouridine, 4-methoxy-pseudouridine, 4-thio-1-methyl-pseudouridine, 4-thio-pseudouridine, 5-aza-uridine, dihydropseudouridine, 5-methoxyuridine and 2'-O-methyl uridine. In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) include a combination of at least two (e.g., 2, 3, 4 or more) of the aforementioned modified nucleobases.

In some embodiments, modified nucleobases in polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) are selected from the group consisting of 1-methyl-pseudouridine ($m^1\psi$), 5-methoxy-uridine (mo^5U), 5-methyl-cytidine (m^5C), pseudouridine (ψ), α-thio-guanosine and α-thio-adenosine. In some embodiments, polynucleotides includes a combination of at least two (e.g., 2, 3, 4 or more) of the aforementioned modified nucleobases.

In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise pseudouridine (v) and 5-methyl-cytidine (m^5C). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise 1-methyl-pseudouridine ($m^1\psi$). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise 1-methyl-pseudouridine ($m^1\psi$) and 5-methyl-cytidine (m^5C). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise 2-thiouridine (s^2U). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise 2-thiouridine and 5-methyl-cytidine (m^5C). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise methoxy-uridine (mo^5U). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise 5-methoxy-uridine (mo^5U) and 5-methyl-cytidine (m^5C). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise 2'-O-methyl uridine. In some embodiments polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise 2'-O-methyl uridine and 5-methyl-cytidine (m^5C). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise N6-methyl-adenosine (m^6A). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise N6-methyl-adenosine (m^6A) and 5-methyl-cytidine (m^5C).

In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) are uniformly modified (e.g., fully modified, modified throughout the entire sequence) for a particular modification. For example, a polynucleotide can be uniformly modified with 5-methyl-cytidine (m^5C), meaning that all cytosine residues in the mRNA sequence are replaced with 5-methyl-cytidine (m^5C).

Similarly, a polynucleotide can be uniformly modified for any type of nucleoside residue present in the sequence by replacement with a modified residue such as those set forth above.

Exemplary nucleobases and nucleosides having a modified cytosine include N4-acetyl-cytidine (ac4C), 5-methyl-cytidine (m5C), 5-halo-cytidine (e.g., 5-iodo-cytidine), 5-hydroxymethyl-cytidine (hm5C), 1-methyl-pseudoisocytidine, 2-thio-cytidine (s2C), and 2-thio-5-methyl-cytidine.

In some embodiments, a modified nucleobase is a modified uridine. Exemplary nucleobases and In some embodiments, a modified nucleobase is a modified cytosine. nucleosides having a modified uridine include 5-cyano uridine, and 4'-thio uridine.

In some embodiments, a modified nucleobase is a modified adenine. Exemplary nucleobases and nucleosides having a modified adenine include 7-deaza-adenine, 1-methyl-adenosine (m1A), 2-methyl-adenine (m2A), and N6-methyl-adenosine (m6A).

In some embodiments, a modified nucleobase is a modified guanine. Exemplary nucleobases and nucleosides having a modified guanine include inosine (I), 1-methyl-inosine (m1I), wyosine (imG), methylwyosine (mimG), 7-deaza-guanosine, 7-cyano-7-deaza-guanosine (preQO), 7-aminomethyl-7-deaza-guanosine (preQ1), 7-methyl-guanosine (m7G), 1-methyl-guanosine (mlG), 8-oxo-guanosine, 7-methyl-8-oxo-guanosine.

The polynucleotides of the present disclosure may be partially or fully modified along the entire length of the molecule. For example, one or more or all or a given type of nucleotide (e.g., purine or pyrimidine, or any one or more or all of A, G, U, C) may be uniformly modified in a polynucleotide of the disclosure, or in a given predetermined sequence region thereof (e.g., in the mRNA including or excluding the polyA tail). In some embodiments, all nucleotides X in a polynucleotide of the present disclosure (or in a given sequence region thereof) are modified nucleotides, wherein X may any one of nucleotides A, G, U, C, or any one of the combinations A+G, A+U, A+C, G+U, G+C, U+C, A+G+U, A+G+C, G+U+C or A+G+C.

The polynucleotide may contain from about 1% to about 100% modified nucleotides (either in relation to overall nucleotide content, or in relation to one or more types of nucleotide, i.e., any one or more of A, G, U or C) or any intervening percentage (e.g., from 1% to 20%, from 1% to 25%, from 1% to 50%, from 1% to 60%, from 1% to 70%, from 1% to 80%, from 1% to 90%, from 1% to 95%, from 10% to 20%, from 10% to 25%, from 10% to 50%, from 10% to 60%, from 10% to 70%, from 10% to 80%, from 10% to 90%, from 10% to 95%, from 10% to 100%, from 20% to 25%, from 20% to 50%, from 20% to 60%, from 20% to 70%, from 20% to 80%, from 20% to 90%, from 20% to 95%, from 20% to 100%, from 50% to 60%, from 50% to 70%, from 50% to 80%, from 50% to 90%, from 50% to 95%, from 50% to 100%, from 70% to 80%, from 70% to 90%, from 70% to 95%, from 70% to 100%, from 80% to 90%, from 80% to 95%, from 80% to 100%, from 90% to 95%, from 90% to 100%, and from 95% to 100%). Any remaining percentage is accounted for by the presence of unmodified A, G, U, or C.

The polynucleotides may contain at a minimum 1% and at maximum 100% modified nucleotides, or any intervening percentage, such as at least 5% modified nucleotides, at least 10% modified nucleotides, at least 25% modified nucleotides, at least 50% modified nucleotides, at least 80% modified nucleotides, or at least 90% modified nucleotides. For example, the polynucleotides may contain a modified pyrimidine such as a modified uracil or cytosine. In some embodiments, at least 5%, at least 10%, at least 25%, at least 50%, at least 80%, at least 90% or 100% of the uracil in the polynucleotide is replaced with a modified uracil (e.g., a 5-substituted uracil). The modified uracil can be replaced by a compound having a single unique structure, or can be replaced by a plurality of compounds having different structures (e.g., 2, 3, 4 or more unique structures). n some embodiments, at least 5%, at least 10%, at least 25%, at least 50%, at least 80%, at least 90% or 100% of the cytosine in the polynucleotide is replaced with a modified cytosine (e.g., a 5-substituted cytosine). The modified cytosine can be replaced by a compound having a single unique structure, or can be replaced by a plurality of compounds having different structures (e.g., 2, 3, 4 or more unique structures).

Thus, in some embodiments, the RNA (e.g., mRNA) vaccines comprise a 5'UTR element, an optionally codon optimized open reading frame, and a 3'UTR element, a poly(A) sequence and/or a polyadenylation signal wherein the RNA is not chemically modified.

In some embodiments, the modified nucleobase is a modified uracil. Exemplary nucleobases and nucleosides having a modified uracil include pseudouridine (ψ), pyridin-4-one ribonucleoside, 5-aza-uridine, 6-aza-uridine, 2-thio-5-aza-uridine, 2-thio-uridine (s^2U), 4-thio-uridine (s^4U), 4-thio-pseudouridine, 2-thio-pseudouridine, 5-hydroxy-uridine (ho^5U), 5-aminoallyl-uridine, 5-halo-uridine (e.g., 5-iodo-uridineor 5-bromo-uridine), 3-methyl-uridine (m^3U), 5-methoxy-uridine (mo^5U), uridine 5-oxyacetic acid (cmo^5U), uridine 5-oxyacetic acid methyl ester ($mcmo^5U$), 5-carboxymethyl-uridine (cm^5U), 1-carboxymethyl-pseudouridine, 5-carboxyhydroxymethyl-uridine (chm^5U), 5-carboxyhydroxymethyl-uridine methyl ester ($mchm^5U$), 5-methoxycarbonylmethyl-uridine (mcm^5U), 5-methoxycarbonylmethyl-2-thio-uridine (mcm^5s^2U), 5-aminomethyl-2-thio-uridine (nm^5s^2U), 5-methylaminomethyl-uridine (mnm^5U), 5-methylaminomethyl-2-thio-uridine (mnm^5s^2U), 5-methylaminomethyl-2-seleno-uridine (mnm^5se^2U), 5-carbamoylmethyl-uridine (ncm^5U), 5-carboxymethylaminomethyl-uridine ($cmnm^5U$), 5-carboxymethylaminomethyl-2-thio-uridine ($cmnm^5s^2U$), 5-propynyl-uridine, 1-propynyl-pseudouridine, 5-taurinomethyl-uridine (τm^5U), 1-taurinomethyl-pseudouridine, 5-taurinomethyl-2-thio-uridine(m^5s^2U), 1-taurinomethyl-4-thio-pseudouridine, 5-methyl-uridine (m^5U, i.e., having the nucleobase deoxythymine), 1-methyl-pseudouridine ($m^1\psi$), 5-methyl-2-thio-uridine ($m5s^2U$), 1-methyl-4-thio-pseudouridine ($m^1s^4\psi$), 4-thio-1-methyl-pseudouridine, 3-methyl-pseudouridine ($m^3\psi$), 2-thio-1-methyl-pseudouridine, 1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-1-deaza-pseudouridine, dihydrouridine (D), dihydropseudouridine, 5,6-dihydrouridine, 5-methyl-dihydrouridine (m^5D), 2-thio-dihydrouridine, 2-thio-dihydropseudouridine, 2-methoxy-uridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, 4-methoxy-2-thio-pseudouridine, N1-methyl-pseudouridine, 3-(3-amino-3-carboxypropyl)uridine (acp^3U), 1-methyl-3-(3-amino-3-carboxypropyl)pseudouridine ($acp^3\psi$), 5-(isopentenylaminomethyl)uridine (inm^5U), 5-(isopentenylaminomethyl)-2-thio-uridine (inm^5s^2U), α-thio-uridine, 2'-O-methyl-uridine (Um), 5,2'-O-dimethyl-uridine (msUm), 2'-O-methyl-pseudouridine (Wm), 2-thio-2'-O-methyl-uridine (s^2Um), 5-methoxycarbonylmethyl-2'-O-methyl-uridine (mcm^5Um), 5-carbamoylmethyl-2'-O-methyl-uridine (ncm^5Um), 5-carboxymethylaminomethyl-2'-O-methyl-uridine ($cmnm^5Um$), 3,2'-O-dimethyl-uridine (m^3Um), and 5-(isopentenylaminomethyl)-2'-O-methyl-uridine (inm^5Um), 1-thio-uridine, deoxythymidine, 2'-F-ara-

uridine, 2'-F-uridine, 2'-OH-ara-uridine, 5-(2-carbomethoxyvinyl) uridine, and 5-[3-(1-E-propenylamino)] uridine.

In some embodiments, the modified nucleobase is a modified cytosine. Exemplary nucleobases and nucleosides having a modified cytosine include 5-aza-cytidine, 6-aza-cytidine, pseudoisocytidine, 3-methyl-cytidine (m^3C), N4-acetyl-cytidine (ac^4C), 5-formyl-cytidine (f^5C), N4-methyl-cytidine (m^4C), 5-methyl-cytidine (m^5C), 5-halo-cytidine (e.g., 5-iodo-cytidine), 5-hydroxymethyl-cytidine (hm^5C), 1-methyl-pseudoisocytidine, pyrrolo-cytidine, pyrrolo-pseudoisocytidine, 2-thio-cytidine (s^2C), 2-thio-5-methyl-cytidine, 4-thio-pseudoisocytidine, 4-thio-1-methyl-pseudoisocytidine, 4-thio-1-methyl-1-deaza-pseudoisocytidine, 1-methyl-1-deaza-pseudoisocytidine, zebularine, 5-aza-zebularine, 5-methyl-zebularine, 5-aza-2-thio-zebularine, 2-thio-zebularine, 2-methoxy-cytidine, 2-methoxy-5-methyl-cytidine, 4-methoxy-pseudoisocytidine, 4-methoxy-1-methyl-pseudoisocytidine, lysidine (k_2C), α-thio-cytidine, 2'-O-methyl-cytidine (Cm), 5,2'-O-dimethyl-cytidine (m^5Cm), N4-acetyl-2'-O-methyl-cytidine (ac^4Cm), N4,2'-O-dimethyl-cytidine (m^4Cm), 5-formyl-2'-O-methyl-cytidine (f^5Cm), N4,N4,2'-O-trimethyl-cytidine (m^42Cm), 1-thio-cytidine, 2'-F-ara-cytidine, 2'-F-cytidine, and 2'-OH-ara-cytidine.

In some embodiments, the modified nucleobase is a modified adenine. Exemplary nucleobases and nucleosides having a modified adenine include 2-amino-purine, 2, 6-diaminopurine, 2-amino-6-halo-purine (e.g., 2-amino-6-chloro-purine), 6-halo-purine (e.g., 6-chloro-purine), 2-amino-6-methyl-purine, 8-azido-adenosine, 7-deaza-adenine, 7-deaza-8-aza-adenine, 7-deaza-2-amino-purine, 7-deaza-8-aza-2-amino-purine, 7-deaza-2,6-diaminopurine, 7-deaza-8-aza-2,6-diaminopurine, 1-methyl-adenosine (m^1A), 2-methyl-adenine (m^2A), N6-methyl-adenosine (m^6A), 2-methylthio-N6-methyl-adenosine (ms^2m^6A), N6-isopentenyl-adenosine (i^6A), 2-methylthio-N6-isopentenyl-adenosine (ms^2i^6A), N6-(cis-hydroxyisopentenyl)adenosine (io^6A), 2-methylthio-N6-(cis-hydroxyisopentenyl) adenosine (ms^2io^6A), N6-glycinylcarbamoyl-adenosine (g^6A), N6-threonylcarbamoyl-adenosine (t^6A), N6-methyl-N6-threonylcarbamoyl-adenosine (m^6t6A), 2-methylthio-N6-threonylcarbamoyl-adenosine (ms^2g^6A), N6,N6-dimethyl-adenosine (m^62A), N6-hydroxynorvalylcarbamoyl-adenosine (hn^6A), 2-methylthio-N6-hydroxynorvalylcarbamoyl-adenosine (ms^2hn^6A), N6-acetyl-adenosine (ac^6A), 7-methyl-adenine, 2-methylthio-adenine, 2-methoxy-adenine, α-thio-adenosine, 2'-O-methyl-adenosine (Am), N6,2'-O-dimethyl-adenosine (m^6Am), N6,N6,2'-O-trimethyl-adenosine (m^62Am), 1,2'-O-dimethyl-adenosine (m^1Am), 2'-O-ribosyladenosine (phosphate) (Ar(p)), 2-amino-N6-methyl-purine, 1-thio-adenosine, 8-azido-adenosine, 2'-F-ara-adenosine, 2'-F-adenosine, 2'-OH-ara-adenosine, and N6-(19-amino-pentaoxanonadecyl)-adenosine.

In some embodiments, the modified nucleobase is a modified guanine. Exemplary nucleobases and nucleosides having a modified guanine include inosine (I), 1-methyl-inosine (m^1I), wyosine (imG), methylwyosine (mimG), 4-demethyl-wyosine (imG-14), isowyosine (imG2), wybutosine (yW), peroxywybutosine (o_2yW), hydroxywybutosine (OhyW), undermodified hydroxywybutosine (OhyW*), 7-deaza-guanosine, queuosine (Q), epoxyqueuosine (oQ), galactosyl-queuosine (galQ), mannosyl-queuosine (manQ), 7-cyano-7-deaza-guanosine ($preQ_0$), 7-aminomethyl-7-deaza-guanosine ($preQ_1$), archaeosine (G^+), 7-deaza-8-aza-guanosine, 6-thio-guanosine, 6-thio-7-deaza-guanosine, 6-thio-7-deaza-8-aza-guanosine, 7-methyl-guanosine (m^7G), 6-thio-7-methyl-guanosine, 7-methyl-inosine, 6-methoxy-guanosine, 1-methyl-guanosine (mG), N2-methyl-guanosine (m^2G), N2,N2-dimethyl-guanosine (m^22G), N2,7-dimethyl-guanosine ($m^{2,7}G$), N2, N2,7-dimethyl-guanosine ($m^{2,2,7}G$), 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, 1-methyl-6-thio-guanosine, N2-methyl-6-thio-guanosine, N2,N2-dimethyl-6-thio-guanosine, α-thio-guanosine, 2'-O-methyl-guanosine (Gm), N2-methyl-2'-O-methyl-guanosine (m^2Gm), N2,N2-dimethyl-2'-O-methyl-guanosine (m^22Gm), 1-methyl-2'-O-methyl-guanosine (mGm), N2,7-dimethyl-2'-O-methyl-guanosine ($m^{2'}7Gm$), 2'-O-methyl-inosine (Im), 1,2'-O-dimethyl-inosine (m^1Im), 2'-O-ribosylguanosine (phosphate) (Gr(p)), 1-thio-guanosine, 06-methyl-guanosine, 2'-F-ara-guanosine, and 2'-F-guanosine.

N-Linked Glycosylation Site Mutants

N-linked glycans of viral proteins play important roles in modulating the immune response. Glycans can be important for maintaining the appropriate antigenic conformations, shielding potential neutralization epitopes, and may alter the proteolytic susceptibility of proteins. Some viruses have putative N-linked glycosylation sites. Deletion or modification of an N-linked glycosylation site may enhance the immune response. Thus, the present disclosure provides, in some embodiments, RNA (e.g., mRNA) vaccines comprising nucleic acids (e.g., mRNA) encoding antigenic polypeptides that comprise a deletion or modification at one or more N-linked glycosylation sites.

In Vitro Transcription of RNA (e.g., mRNA)

Respiratory virus vaccines of the present disclosure comprise at least one RNA polynucleotide, such as a mRNA (e.g., modified mRNA). mRNA, for example, is transcribed in vitro from template DNA, referred to as an "in vitro transcription template." In some embodiments, an in vitro transcription template encodes a 5' untranslated (UTR) region, contains an open reading frame, and encodes a 3' UTR and a polyA tail. The particular nucleic acid sequence composition and length of an in vitro transcription template will depend on the mRNA encoded by the template.

A "5' untranslated region" (5'UTR) refers to a region of an mRNA that is directly upstream (i.e., 5') from the start codon (i.e., the first codon of an mRNA transcript translated by a ribosome) that does not encode a polypeptide.

A "3' untranslated region" (3'UTR) refers to a region of an mRNA that is directly downstream (i.e., 3') from the stop codon (i.e., the codon of an mRNA transcript that signals a termination of translation) that does not encode a polypeptide.

An "open reading frame" is a continuous stretch of DNA beginning with a start codon (e.g., methionine (ATG)), and ending with a stop codon (e.g., TAA, TAG or TGA) and encodes a polypeptide.

A "polyA tail" is a region of mRNA that is downstream, e.g., directly downstream (i.e., 3'), from the 3' UTR that contains multiple, consecutive adenosine monophosphates. A polyA tail may contain 10 to 300 adenosine monophosphates. For example, a polyA tail may contain 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290 or 300 adenosine monophosphates. In some embodiments, a polyA tail contains 50 to 250 adenosine monophosphates. In a relevant biological setting (e.g., in cells, in vivo) the poly(A) tail functions to protect mRNA from enzymatic degradation, e.g., in the cytoplasm, and aids in transcription termination, export of the mRNA from the nucleus and translation.

In some embodiments, a polynucleotide includes 200 to 3,000 nucleotides. For example, a polynucleotide may include 200 to 500, 200 to 1000, 200 to 1500, 200 to 3000, 500 to 1000, 500 to 1500, 500 to 2000, 500 to 3000, 1000 to 1500, 1000 to 2000, 1000 to 3000, 1500 to 3000, or 2000 to 3000 nucleotides.

Flagellin Adjuvants

Flagellin is an approximately 500 amino acid monomeric protein that polymerizes to form the flagella associated with bacterial motion. Flagellin is expressed by a variety of flagellated bacteria (*Salmonella typhimurium* for example) as well as non-flagellated bacteria (such as *Escherichia coli*). Sensing of flagellin by cells of the innate immune system (dendritic cells, macrophages, etc.) is mediated by the Toll-like receptor 5 (TLR5) as well as by Nod-like receptors (NLRs) Ipaf and Naip5. TLRs and NLRs have been identified as playing a role in the activation of innate immune response and adaptive immune response. As such, flagellin provides an adjuvant effect in a vaccine.

The nucleotide and amino acid sequences encoding known flagellin polypeptides are publicly available in the NCBI GenBank database. The flagellin sequences from S. *Typhimurium, H. Pylori, V. Cholera, S. marcesens, S. flexneri, T. Pallidum, L. pneumophila, B. burgdorferei, C. difficile, R. meliloti, A. tumefaciens, R. lupini, B. clarridgeiae, P. Mirabilis, B. subtilus, L. monocytogenes, P. aeruginosa*, and *E. coli*, among others are known.

A flagellin polypeptide, as used herein, refers to a full length flagellin protein, immunogenic fragments thereof, and peptides having at least 50% sequence identify to a flagellin protein or immunogenic fragments thereof. Exemplary flagellin proteins include flagellin from *Salmonella typhi* (UniPro Entry number: Q56086), *Salmonella typhimurium* (A0A0C9DG09), *Salmonella enteritidis* (AOAOC9BAB7), and *Salmonella choleraesuis* (Q6V2X8), and SEQ ID NO: 54-56 (Table 17). In some embodiments, the flagellin polypeptide has at least 60%, 70%, 75%, 80%, 90%, 95%, 97%, 98%, or 99% sequence identify to a flagellin protein or immunogenic fragments thereof.

In some embodiments, the flagellin polypeptide is an immunogenic fragment. An immunogenic fragment is a portion of a flagellin protein that provokes an immune response. In some embodiments, the immune response is a TLR5 immune response. An example of an immunogenic fragment is a flagellin protein in which all or a portion of a hinge region has been deleted or replaced with other amino acids. For example, an antigenic polypeptide may be inserted in the hinge region. Hinge regions are the hypervariable regions of a flagellin. Hinge regions of a flagellin are also referred to as "D3 domain or region, "propeller domain or region," "hypervariable domain or region" and "variable domain or region." "At least a portion of a hinge region," as used herein, refers to any part of the hinge region of the flagellin, or the entirety of the hinge region. In other embodiments an immunogenic fragment of flagellin is a 20, 25, 30, 35, or 40 amino acid C-terminal fragment of flagellin.

The flagellin monomer is formed by domains D0 through D3. D0 and D1, which form the stem, are composed of tandem long alpha helices and are highly conserved among different bacteria. The D1 domain includes several stretches of amino acids that are useful for TLR5 activation. The entire D1 domain or one or more of the active regions within the domain are immunogenic fragments of flagellin. Examples of immunogenic regions within the D1 domain include residues 88-114 and residues 411-431 (in *Salmonella typhimurium* FliC flagellin. Within the 13 amino acids in the 88-100 region, at least 6 substitutions are permitted between *Salmonella* flagellin and other flagellins that still preserve TLR5 activation. Thus, immunogenic fragments of flagellin include flagellin like sequences that activate TLR5 and contain a 13 amino acid motif that is 53% or more identical to the *Salmonella* sequence in 88-100 of FliC (LQRVRELAVQSAN; SEQ ID NO: 84).

In some embodiments, the RNA (e.g., mRNA) vaccine includes an RNA that encodes a fusion protein of flagellin and one or more antigenic polypeptides. A "fusion protein" as used herein, refers to a linking of two components of the construct. In some embodiments, a carboxy-terminus of the antigenic polypeptide is fused or linked to an amino terminus of the flagellin polypeptide. In other embodiments, an amino-terminus of the antigenic polypeptide is fused or linked to a carboxy-terminus of the flagellin polypeptide. The fusion protein may include, for example, one, two, three, four, five, six or more flagellin polypeptides linked to one, two, three, four, five, six or more antigenic polypeptides. When two or more flagellin polypeptides and/or two or more antigenic polypeptides are linked such a construct may be referred to as a "multimer."

Each of the components of a fusion protein may be directly linked to one another or they may be connected through a linker. For instance, the linker may be an amino acid linker. The amino acid linker encoded for by the RNA (e.g., mRNA) vaccine to link the components of the fusion protein may include, for instance, at least one member selected from the group consisting of a lysine residue, a glutamic acid residue, a serine residue and an arginine residue. In some embodiments the linker is 1-30, 1-25, 1-25, 5-10, 5, 15, or 5-20 amino acids in length.

In other embodiments the RNA (e.g., mRNA) vaccine includes at least two separate RNA polynucleotides, one encoding one or more antigenic polypeptides and the other encoding the flagellin polypeptide. The at least two RNA polynucleotides may be co-formulated in a carrier such as a lipid nanoparticle.

Broad Spectrum RNA (e.g., mRNA) Vaccines

There may be situations where persons are at risk for infection with more than one strain of hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1). RNA (e.g., mRNA) therapeutic vaccines are particularly amenable to combination vaccination approaches due to a number of factors including, but not limited to, speed of manufacture, ability to rapidly tailor vaccines to accommodate perceived geographical threat, and the like. Moreover, because the vaccines utilize the human body to produce the antigenic protein, the vaccines are amenable to the production of larger, more complex antigenic proteins, allowing for proper folding, surface expression, antigen presentation, etc. in the human subject. To protect against more than one strain of hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1), a combination vaccine can be administered that includes RNA (e.g., mRNA) encoding at least one antigenic polypeptide protein (or antigenic portion thereof) of a first respiratory virus and further includes RNA encoding at least one antigenic polypeptide protein (or antigenic portion thereof) of a second respiratory virus. RNA (e.g., mRNA) can be co-formulated, for example, in a single lipid nanoparticle (LNP) or can be formulated in separate LNPs for co-administration.

Methods of Treatment

Provided herein are compositions (e.g., pharmaceutical compositions), methods, kits and reagents for prevention and/or treatment of respiratory diseases/infections in humans and other mammals. Respiratory virus RNA (e.g. mRNA) vaccines can be used as therapeutic or prophylactic agents, alone or in combination with other vaccine(s). They may be used in medicine to prevent and/or treat respiratory disease/infection. In exemplary aspects, the RNA (e.g., mRNA) vaccines of the present disclosure are used to provide prophylactic protection from hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1). Prophylactic protection from hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) can be achieved following administration of a RNA (e.g., mRNA) vaccine of the present disclosure. Respiratory virus RNA (e.g., mRNA) vaccines of the present disclosure may be used to treat or prevent viral "co-infections" containing two or more respiratory infections. Vaccines can be administered once, twice, three times, four times or more, but it is likely sufficient to administer the vaccine once (optionally followed by a single booster). It is possible, although less desirable, to administer the vaccine to an infected individual to achieve a therapeutic response. Dosing may need to be adjusted accordingly.

A method of eliciting an immune response in a subject against hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) is provided in aspects of the present disclosure. The method involves administering to the subject a respiratory virus RNA (e.g., mRNA) vaccine comprising at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) antigenic polypeptide thereof, thereby inducing in the subject an immune response specific to hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) antigenic polypeptide or an immunogenic fragment thereof, wherein anti-antigenic polypeptide antibody titer in the subject is increased following vaccination relative to anti-antigenic polypeptide antibody titer in a subject vaccinated with a prophylactically effective dose of a traditional vaccine against hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1). An "anti-antigenic polypeptide antibody" is a serum antibody the binds specifically to the antigenic polypeptide.

In some embodiments, a RNA (e.g., mRNA) vaccine (e.g., a hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1 RNA vaccine) capable of eliciting an immune response is administered intramuscularly via a composition including a compound according to Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe) (e.g., Compound 3, 18, 20, 25, 26, 29, 30, 60, 108-112, or 122).

A prophylactically effective dose is a therapeutically effective dose that prevents infection with the virus at a clinically acceptable level. In some embodiments the therapeutically effective dose is a dose listed in a package insert for the vaccine. A traditional vaccine, as used herein, refers to a vaccine other than the RNA (e.g., mRNA) vaccines of the present disclosure. For instance, a traditional vaccine includes but is not limited to live/attenuated microorganism vaccines, killed/inactivated microorganism vaccines, subunit vaccines, protein antigen vaccines, DNA vaccines, VLP vaccines, etc. In exemplary embodiments, a traditional vaccine is a vaccine that has achieved regulatory approval and/or is registered by a national drug regulatory body, for example the Food and Drug Administration (FDA) in the United States or the European Medicines Agency (EMA).

In some embodiments the anti-antigenic polypeptide antibody titer in the subject is increased 1 log to 10 log following vaccination relative to anti-antigenic polypeptide antibody titer in a subject vaccinated with a prophylactically effective dose of a traditional vaccine against hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1).

In some embodiments the anti-antigenic polypeptide antibody titer in the subject is increased 1 log, 2 log, 3 log, 5 log or 10 log following vaccination relative to anti-antigenic polypeptide antibody titer in a subject vaccinated with a prophylactically effective dose of a traditional vaccine against hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1).

A method of eliciting an immune response in a subject against hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) is provided in other aspects of the disclosure. The method involves administering to the subject a respiratory virus RNA (e.g., mRNA) vaccine comprising at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) antigenic polypeptide or an immunogenic fragment thereof, thereby inducing in the subject an immune response specific to hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) antigenic polypeptide or an immunogenic fragment thereof, wherein the immune response in the subject is equivalent to an immune response in a subject vaccinated with a traditional vaccine against the hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) at 2 times to 100 times the dosage level relative to the RNA (e.g., mRNA) vaccine.

In some embodiments, the immune response in the subject is equivalent to an immune response in a subject vaccinated with a traditional vaccine at 2, 3, 4, 5, 10, 50, 100 times the dosage level relative to the hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) RNA (e.g., mRNA) vaccine.

In some embodiments the immune response in the subject is equivalent to an immune response in a subject vaccinated with a traditional vaccine at 10-100 times, or 100-1000 times, the dosage level relative to the hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV,

HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) RNA (e.g., mRNA) vaccine.

In some embodiments the immune response is assessed by determining [protein] antibody titer in the subject.

Some aspects of the present disclosure provide a method of eliciting an immune response in a subject against a In some embodiments the immune response in the subject is equivalent to an immune response in a subject vaccinated with a traditional vaccine at 2, 3, 4, 5, 10, 50, 100 times the dosage level relative to the hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) RNA (e.g., mRNA) vaccine by administering to the subject a respiratory virus RNA (e.g., mRNA) vaccine comprising at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) antigenic polypeptide, thereby inducing in the subject an immune response specific to the antigenic polypeptide or an immunogenic fragment thereof, wherein the immune response in the subject is induced 2 days to 10 weeks earlier relative to an immune response induced in a subject vaccinated with a prophylactically effective dose of a traditional vaccine against the hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1). In some embodiments, the immune response in the subject is induced in a subject vaccinated with a prophylactically effective dose of a traditional vaccine at 2 times to 100 times the dosage level relative to the RNA (e.g., mRNA) vaccine.

In some embodiments, the immune response in the subject is induced 2 days earlier, or 3 days earlier, relative to an immune response induced in a subject vaccinated with a prophylactically effective dose of a traditional vaccine.

In some embodiments the immune response in the subject is induced 1 week, 2 weeks, 3 weeks, 5 weeks, or 10 weeks earlier relative to an immune response induced in a subject vaccinated with a prophylactically effective dose of a traditional vaccine.

Also provided herein is a method of eliciting an immune response in a subject against hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) by administering to the subject a respiratory virus RNA (e.g., mRNA) vaccine having an open reading frame encoding a first antigenic polypeptide, wherein the RNA polynucleotide does not include a stabilization element, and wherein an adjuvant is not co-formulated or co-administered with the vaccine.

Therapeutic and Prophylactic Compositions

Provided herein are compositions (e.g., pharmaceutical compositions), methods, kits and reagents for prevention, treatment or diagnosis of hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) in humans and other mammals, for example. Respiratory virus RNA (e.g. mRNA) vaccines can be used as therapeutic or prophylactic agents. They may be used in medicine to prevent and/or treat infectious disease. In some embodiments, the respiratory RNA (e.g., mRNA) vaccines of the present disclosure are used fin the priming of immune effector cells, for example, to activate peripheral blood mononuclear cells (PBMCs) ex vivo, which are then infused (re-infused) into a subject.

In some embodiments, respiratory virus vaccine containing RNA (e.g., mRNA) polynucleotides as described herein can be administered to a subject (e.g., a mammalian subject, such as a human subject), and the RNA (e.g., mRNA) polynucleotides are translated in vivo to produce an antigenic polypeptide.

The respiratory virus RNA (e.g., mRNA) vaccines may be induced for translation of a polypeptide (e.g., antigen or immunogen) in a cell, tissue or organism. In some embodiments, such translation occurs in vivo, although such translation may occur ex vivo, in culture or in vitro. In some embodiments, the cell, tissue or organism is contacted with an effective amount of a composition containing a respiratory virus RNA (e.g., mRNA) vaccine that contains a polynucleotide that has at least one a translatable region encoding an antigenic polypeptide.

An "effective amount" of an respiratory virus RNA (e.g. mRNA) vaccine is provided based, at least in part, on the target tissue, target cell type, means of administration, physical characteristics of the polynucleotide (e.g., size, and extent of modified nucleosides) and other components of the vaccine, and other determinants. In general, an effective amount of the respiratory virus RNA (e.g., mRNA) vaccine composition provides an induced or boosted immune response as a function of antigen production in the cell, preferably more efficient than a composition containing a corresponding unmodified polynucleotide encoding the same antigen or a peptide antigen. Increased antigen production may be demonstrated by increased cell transfection (the percentage of cells transfected with the RNA, e.g., mRNA, vaccine), increased protein translation from the polynucleotide, decreased nucleic acid degradation (as demonstrated, for example, by increased duration of protein translation from a modified polynucleotide), or altered antigen specific immune response of the host cell.

In some embodiments, RNA (e.g. mRNA) vaccines (including polynucleotides their encoded polypeptides) in accordance with the present disclosure may be used for treatment of hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1).

Respiratory RNA (e.g. mRNA) vaccines may be administered prophylactically or therapeutically as part of an active immunization scheme to healthy individuals or early in infection during the incubation phase or during active infection after onset of symptoms. In some embodiments, the amount of RNA (e.g., mRNA) vaccine of the present disclosure provided to a cell, a tissue or a subject may be an amount effective for immune prophylaxis.

Respiratory virus RNA (e.g. mRNA) vaccines may be administrated with other prophylactic or therapeutic compounds. As a non-limiting example, a prophylactic or therapeutic compound may be an adjuvant or a booster. As used herein, when referring to a prophylactic composition, such as a vaccine, the term "booster" refers to an extra administration of the prophylactic (vaccine) composition. A booster (or booster vaccine) may be given after an earlier administration of the prophylactic composition. The time of administration between the initial administration of the prophylactic composition and the booster may be, but is not limited to, 1 minute, 2 minutes, 3 minutes, 4 minutes, 5 minutes, 6 minutes, 7 minutes, 8 minutes, 9 minutes, 10 minutes, 15 minutes, 20 minutes 35 minutes, 40 minutes, 45 minutes, 50 minutes, 55 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5

hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 1 day, 36 hours, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 10 days, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 18 months, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, 12 years, 13 years, 14 years, 15 years, 16 years, 17 years, 18 years, 19 years, 20 years, 25 years, 30 years, 35 years, 40 years, 45 years, 50 years, 55 years, 60 years, 65 years, 70 years, 75 years, 80 years, 85 years, 90 years, 95 years or more than 99 years. In some embodiments, the time of administration between the initial administration of the prophylactic composition and the booster may be, but is not limited to, 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 6 months or 1 year.

In some embodiments, respiratory virus RNA (e.g. mRNA) vaccines may be administered intramuscularly or intradermally, similarly to the administration of inactivated vaccines known in the art.

Respiratory virus RNA (e.g. mRNA) vaccines may be utilized in various settings depending on the prevalence of the infection or the degree or level of unmet medical need. As a non-limiting example, the RNA (e.g., mRNA) vaccines may be utilized to treat and/or prevent a variety of respiratory infections. RNA (e.g., mRNA) vaccines have superior properties in that they produce much larger antibody titers and produce responses early than commercially available anti-viral agents/compositions.

Provided herein are pharmaceutical compositions including respiratory virus RNA (e.g. mRNA) vaccines and RNA (e.g. mRNA) vaccine compositions and/or complexes optionally in combination with one or more pharmaceutically acceptable excipients.

Respiratory virus RNA (e.g. mRNA) vaccines may be formulated or administered alone or in conjunction with one or more other components. For instance, hMPV/PIV3/RSV RNA (e.g., mRNA) vaccines (vaccine compositions) may comprise other components including, but not limited to, adjuvants.

In some embodiments, respiratory virus (e.g. mRNA) vaccines do not include an adjuvant (they are adjuvant free).

Respiratory virus RNA (e.g. mRNA) vaccines may be formulated or administered in combination with one or more pharmaceutically-acceptable excipients. In some embodiments, vaccine compositions comprise at least one additional active substances, such as, for example, a therapeutically-active substance, a prophylactically-active substance, or a combination of both. Vaccine compositions may be sterile, pyrogen-free or both sterile and pyrogen-free. General considerations in the formulation and/or manufacture of pharmaceutical agents, such as vaccine compositions, may be found, for example, in Remington: The Science and Practice of Pharmacy 21st ed., Lippincott Williams & Wilkins, 2005 (incorporated herein by reference in its entirety).

In some embodiments, respiratory virus RNA (e.g. mRNA) vaccines are administered to humans, human patients or subjects. For the purposes of the present disclosure, the phrase "active ingredient" generally refers to the RNA (e.g., mRNA) vaccines or the polynucleotides contained therein, for example, RNA polynucleotides (e.g., mRNA polynucleotides) encoding antigenic polypeptides.

Formulations of the respiratory virus vaccine compositions described herein may be prepared by any method known or hereafter developed in the art of pharmacology. In general, such preparatory methods include the step of bringing the active ingredient (e.g., mRNA polynucleotide) into association with an excipient and/or one or more other accessory ingredients, and then, if necessary and/or desirable, dividing, shaping and/or packaging the product into a desired single- or multi-dose unit.

Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition in accordance with the disclosure will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100%, e.g., between 0.5 and 50%, between 1-30%, between 5-80%, at least 80% (w/w) active ingredient.

Respiratory virus RNA (e.g. mRNA) vaccines can be formulated using one or more excipients to: (1) increase stability; (2) increase cell transfection; (3) permit the sustained or delayed release (e.g., from a depot formulation); (4) alter the biodistribution (e.g., target to specific tissues or cell types); (5) increase the translation of encoded protein in vivo; and/or (6) alter the release profile of encoded protein (antigen) in vivo. In addition to traditional excipients such as any and all solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, excipients can include, without limitation, lipidoids, liposomes, lipid nanoparticles, polymers, lipoplexes, core-shell nanoparticles, peptides, proteins, cells transfected with respiratory virus RNA (e.g. mRNA)vaccines (e.g., for transplantation into a subject), hyaluronidase, nanoparticle mimics and combinations thereof.

Stabilizing Elements

Naturally-occurring eukaryotic mRNA molecules have been found to contain stabilizing elements, including, but not limited to untranslated regions (UTR) at their 5'-end (5'UTR) and/or at their 3'-end (3'UTR), in addition to other structural features, such as a 5'-cap structure or a 3'-poly(A) tail. Both the 5'UTR and the 3'UTR are typically transcribed from the genomic DNA and are elements of the premature mRNA. Characteristic structural features of mature mRNA, such as the 5'-cap and the 3'-poly(A) tail are usually added to the transcribed (premature) mRNA during mRNA processing. The 3'-poly(A) tail is typically a stretch of adenine nucleotides added to the 3'-end of the transcribed mRNA. It can comprise up to about 400 adenine nucleotides. In some embodiments the length of the 3'-poly(A) tail may be an essential element with respect to the stability of the individual mRNA.

In some embodiments the RNA (e.g., mRNA) vaccine may include one or more stabilizing elements. Stabilizing elements may include for instance a histone stem-loop. A stem-loop binding protein (SLBP), a 32 kDa protein has been identified. It is associated with the histone stem-loop at the 3'-end of the histone messages in both the nucleus and the cytoplasm. Its expression level is regulated by the cell cycle; it peaks during the S-phase, when histone mRNA levels are also elevated. The protein has been shown to be essential for efficient 3'-end processing of histone pre-mRNA by the U7 snRNP. SLBP continues to be associated with the stem-loop after processing, and then stimulates the translation of mature histone mRNAs into histone proteins in the cytoplasm. The RNA binding domain of SLBP is conserved through metazoa and protozoa; its binding to the histone stem-loop depends on the structure of the loop. The

minimum binding site includes at least three nucleotides 5' and two nucleotides 3' relative to the stem-loop.

In some embodiments, the RNA (e.g., mRNA) vaccines include a coding region, at least one histone stem-loop, and optionally, a poly(A) sequence or polyadenylation signal. The poly(A) sequence or polyadenylation signal generally should enhance the expression level of the encoded protein. The encoded protein, in some embodiments, is not a histone protein, a reporter protein (e.g. Luciferase, GFP, EGFP, β-Galactosidase, EGFP), or a marker or selection protein (e.g. alpha-Globin, Galactokinase and Xanthine:guanine phosphoribosyl transferase (GPT)).

In some embodiments, the combination of a poly(A) sequence or polyadenylation signal and at least one histone stem-loop, even though both represent alternative mechanisms in nature, acts synergistically to increase the protein expression beyond the level observed with either of the individual elements. It has been found that the synergistic effect of the combination of poly(A) and at least one histone stem-loop does not depend on the order of the elements or the length of the poly(A) sequence.

In some embodiments, the RNA (e.g., mRNA) vaccine does not comprise a histone downstream element (HDE). "Histone downstream element" (HDE) includes a purine-rich polynucleotide stretch of approximately 15 to 20 nucleotides 3' of naturally occurring stem-loops, representing the binding site for the U7 snRNA, which is involved in processing of histone pre-mRNA into mature histone mRNA. Ideally, the inventive nucleic acid does not include an intron.

In some embodiments, the RNA (e.g., mRNA) vaccine may or may not contain a enhancer and/or promoter sequence, which may be modified or unmodified or which may be activated or inactivated. In some embodiments, the histone stem-loop is generally derived from histone genes, and includes an intramolecular base pairing of two neighbored partially or entirely reverse complementary sequences separated by a spacer, including (e.g., consisting of) a short sequence, which forms the loop of the structure. The unpaired loop region is typically unable to base pair with either of the stem loop elements. It occurs more often in RNA, as is a key component of many RNA secondary structures, but may be present in single-stranded DNA as well. Stability of the stem-loop structure generally depends on the length, number of mismatches or bulges, and base composition of the paired region. In some embodiments, wobble base pairing (non-Watson-Crick base pairing) may result. In some embodiments, the at least one histone stem-loop sequence comprises a length of 15 to 45 nucleotides.

In other embodiments the RNA (e.g., mRNA) vaccine may have one or more AU-rich sequences removed. These sequences, sometimes referred to as AURES are destabilizing sequences found in the 3'UTR. The AURES may be removed from the RNA (e.g., mRNA) vaccines. Alternatively the AURES may remain in the RNA (e.g., mRNA) vaccine.

Nanoparticle Formulations

In some embodiments, respiratory virus RNA (e.g. mRNA) vaccines are formulated in a nanoparticle. In some embodiments, respiratory virus RNA (e.g. mRNA) vaccines are formulated in a lipid nanoparticle. In some embodiments, respiratory virus RNA (e.g. mRNA) vaccines are formulated in a lipid-polycation complex, referred to as a cationic lipid nanoparticle. As a non-limiting example, the polycation may include a cationic peptide or a polypeptide such as, but not limited to, polylysine, polyornithine and/or polyarginine. In some embodiments, respiratory virus RNA (e.g., mRNA) vaccines are formulated in a lipid nanoparticle that includes a non-cationic lipid such as, but not limited to, cholesterol or dioleoyl phosphatidylethanolamine (DOPE).

A lipid nanoparticle formulation may be influenced by, but not limited to, the selection of the cationic lipid component, the degree of cationic lipid saturation, the nature of the PEGylation, ratio of all components and biophysical parameters such as size. In one example by Semple et al. (*Nature Biotech.* 2010 28:172-176), the lipid nanoparticle formulation is composed of 57.1% cationic lipid, 7.1% dipalmitoylphosphatidylcholine, 34.3% cholesterol, and 1.4% PEG-c-DMA. As another example, changing the composition of the cationic lipid can more effectively deliver siRNA to various antigen presenting cells (Basha et al. *Mol Ther.* 2011 19:2186-2200).

In some embodiments, lipid nanoparticle formulations may comprise 35 to 45% cationic lipid, 40% to 50% cationic lipid, 50% to 60% cationic lipid and/or 55% to 65% cationic lipid. In some embodiments, the ratio of lipid to RNA (e.g., mRNA) in lipid nanoparticles may be 5:1 to 20:1, 10:1 to 25:1, 15:1 to 30:1 and/or at least 30:1.

In some embodiments, the ratio of PEG in the lipid nanoparticle formulations may be increased or decreased and/or the carbon chain length of the PEG lipid may be modified from C14 to C18 to alter the pharmacokinetics and/or biodistribution of the lipid nanoparticle formulations. As a non-limiting example, lipid nanoparticle formulations may contain 0.5% to 3.0%, 1.0% to 3.5%, 1.5% to 4.0%, 2.0% to 4.5%, 2.5% to 5.0% and/or 3.0% to 6.0% of the lipid molar ratio of PEG-c-DOMG (R-3-[(ω-methoxy-poly(ethyleneglycol)2000)carbamoyl)]-1,2-dimyristyloxypropyl-3-amine) (also referred to herein as PEG-DOMG) as compared to the cationic lipid, DSPC and cholesterol. In some embodiments, the PEG-c-DOMG may be replaced with a PEG lipid such as, but not limited to, PEG-DSG (1,2-Distearoyl-sn-glycerol, methoxypolyethylene glycol), PEG-DMG (1,2-Dimyristoyl-sn-glycerol) and/or PEG-DPG (1,2-Dipalmitoyl-sn-glycerol, methoxypolyethylene glycol). The cationic lipid may be selected from any lipid known in the art such as, but not limited to, DLin-MC3-DMA, DLin-DMA, C12-200 and DLin-KC2-DMA.

In some embodiments, an respiratory virus RNA (e.g. mRNA) vaccine formulation is a nanoparticle that comprises at least one lipid. The lipid may be selected from, but is not limited to, DLin-DMA, DLin-K-DMA, 98N12-5, C12-200, DLin-MC3-DMA, DLin-KC2-DMA, DODMA, PLGA, PEG, PEG-DMG, PEGylated lipids and amino alcohol lipids. In some embodiments, the lipid may be a cationic lipid such as, but not limited to, DLin-DMA, DLin-D-DMA, DLin-MC3-DMA, DLin-KC2-DMA, DODMA and amino alcohol lipids.

The amino alcohol cationic lipid may be the lipids described in and/or made by the methods described in U.S. Patent Publication No. US20130150625, herein incorporated by reference in its entirety. As a non-limiting example, the cationic lipid may be 2-amino-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-2-{[(9Z,2Z)-octadeca-9,12-dien-1-yloxy]methyl}propan-1-ol (Compound 1 in US20130150625); 2-amino-3-[(9Z)-octadec-9-en-1-yloxy]-2-{[(9Z)-octadec-9-en-1-yloxy]methyl}propan-1-ol (Compound 2 in US20130150625); 2-amino-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-2-[(octyloxy)methyl]propan-1-ol (Compound 3 in US20130150625); and 2-(dimethylamino)-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-2-{[(9Z, 12Z)-octadeca-9,12-dien-1-yloxy]methyl}propan-1-ol (Compound 4 in US20130150625); or any pharmaceutically acceptable salt or stereoisomer thereof.

Lipid nanoparticle formulations typically comprise a lipid, in particular, an ionizable cationic lipid, for example, 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), or di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), and further comprise a neutral lipid, a sterol and a molecule capable of reducing particle aggregation, for example a PEG or PEG-modified lipid.

In some embodiments, a lipid nanoparticle formulation consists essentially of (i) at least one lipid selected from the group consisting of 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy) heptadecanedioate (L319); (ii) a neutral lipid selected from DSPC, DPPC, POPC, DOPE and SM; (iii) a sterol, e.g., cholesterol; and (iv) a PEG-lipid, e.g., PEG-DMG or PEG-cDMA, in a molar ratio of 20-60% cationic lipid: 5-25% neutral lipid: 25-55% sterol; 0.5-15% PEG-lipid.

In some embodiments, a lipid nanoparticle formulation includes 25% to 75% on a molar basis of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), e.g., 35 to 65%, 45 to 65%, 60%, 57.5%, 50% or 40% on a molar basis.

In some embodiments, a lipid nanoparticle formulation includes 0.5% to 15% on a molar basis of the neutral lipid, e.g., 3 to 12%, 5 to 10% or 15%, 10%, or 7.5% on a molar basis. Examples of neutral lipids include, without limitation, DSPC, POPC, DPPC, DOPE and SM. In some embodiments, the formulation includes 5% to 50% on a molar basis of the sterol (e.g., 15 to 45%, 20 to 40%, 40%, 38.5%, 35%, or 31% on a molar basis. A non-limiting example of a sterol is cholesterol. In some embodiments, a lipid nanoparticle formulation includes 0.5% to 20% on a molar basis of the PEG or PEG-modified lipid (e.g., 0.5 to 10%, 0.5 to 5%, 1.5%, 0.5%, 1.5%, 3.5%, or 5% on a molar basis. In some embodiments, a PEG or PEG modified lipid comprises a PEG molecule of an average molecular weight of 2,000 Da. In some embodiments, a PEG or PEG modified lipid comprises a PEG molecule of an average molecular weight of less than 2,000, for example around 1,500 Da, around 1,000 Da, or around 500 Da. Non-limiting examples of PEG-modified lipids include PEG-distearoyl glycerol (PEG-DMG) (also referred herein as PEG-C14 or C14-PEG), PEG-cDMA (further discussed in Reyes et al. J. Controlled Release, 107, 276-287 (2005) the contents of which are herein incorporated by reference in their entirety).

In some embodiments, lipid nanoparticle formulations include 25-75% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 0.5-15% of the neutral lipid, 5-50% of the sterol, and 0.5-20% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 35-65% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 3-12% of the neutral lipid, 15-45% of the sterol, and 0.5-10% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 45-65% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 5-10% of the neutral lipid, 25-40% of the sterol, and 0.5-10% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 60% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 7.5% of the neutral lipid, 31% of the sterol, and 1.5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 50% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 10% of the neutral lipid, 38.5% of the sterol, and 1.5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 50% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 10% of the neutral lipid, 35% of the sterol, 4.5% or 5% of the PEG or PEG-modified lipid, and 0.5% of the targeting lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 40% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 15% of the neutral lipid, 40% of the sterol, and 5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 57.2% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 7.1% of the neutral lipid, 34.3% of the sterol, and 1.4% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 57.5% of a cationic lipid selected from the PEG lipid is PEG-cDMA (PEG-cDMA is further discussed in Reyes et al. (J. Controlled Release, 107, 276-287 (2005), the contents of which are herein incorporated by reference in their entirety), 7.5% of the neutral lipid, 31.5% of the sterol, and 3.5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations consists essentially of a lipid mixture in molar ratios of 20-70% cationic lipid: 5-45% neutral lipid: 20-55% cholesterol: 0.5-15% PEG-modified lipid. In some embodiments, lipid nanoparticle formulations consists essentially of a lipid mixture in a molar ratio of 20-60% cationic lipid: 5-25% neutral lipid: 25-55% cholesterol: 0.5-15% PEG-modified lipid.

In some embodiments, the molar lipid ratio is 50/10/38.5/1.5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG, PEG-DSG or PEG-

DPG), 57.2/7.1134.3/1.4 (mol % cationic lipid/neutral lipid, e.g., DPPC/Chol/PEG-modified lipid, e.g., PEG-cDMA), 40/15/40/5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG), 50/10/35/4.5/0.5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DSG), 50/10/35/5 (cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG), 40/10/40/10 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG or PEG-cDMA), 35/15/40/10 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG or PEG-cDMA) or 52/13/30/5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG or PEG-cDMA).

Non-limiting examples of lipid nanoparticle compositions and methods of making them are described, for example, in Semple et al. (2010) *Nat. Biotechnol.* 28:172-176; Jayarama et al. (2012), *Angew. Chem. Int. Ed.,* 51: 8529-8533; and Maier et al. (2013) *Molecular Therapy* 21, 1570-1578 (the contents of each of which are incorporated herein by reference in their entirety).

In some embodiments, lipid nanoparticle formulations may comprise a cationic lipid, a PEG lipid and a structural lipid and optionally comprise a non-cationic lipid. As a non-limiting example, a lipid nanoparticle may comprise 40-60% of cationic lipid, 5-15% of a non-cationic lipid, 1-2% of a PEG lipid and 30-50% of a structural lipid. As another non-limiting example, the lipid nanoparticle may comprise 50% cationic lipid, 10% non-cationic lipid, 1.5% PEG lipid and 38.5% structural lipid. As yet another non-limiting example, a lipid nanoparticle may comprise 55% cationic lipid, 10% non-cationic lipid, 2.5% PEG lipid and 32.5% structural lipid. In some embodiments, the cationic lipid may be any cationic lipid described herein such as, but not limited to, DLin-KC2-DMA, DLin-MC3-DMA and L319.

In some embodiments, the lipid nanoparticle formulations described herein may be 4 component lipid nanoparticles. The lipid nanoparticle may comprise a cationic lipid, a non-cationic lipid, a PEG lipid and a structural lipid. As a non-limiting example, the lipid nanoparticle may comprise 40-60% of cationic lipid, 5-15% of a non-cationic lipid, 1-2% of a PEG lipid and 30-50% of a structural lipid. As another non-limiting example, the lipid nanoparticle may comprise 50% cationic lipid, 10% non-cationic lipid, 1.5% PEG lipid and 38.5% structural lipid. As yet another non-limiting example, the lipid nanoparticle may comprise 55% cationic lipid, 10% non-cationic lipid, 2.5% PEG lipid and 32.5% structural lipid. In some embodiments, the cationic lipid may be any cationic lipid described herein such as, but not limited to, DLin-KC2-DMA, DLin-MC3-DMA and L319.

In some embodiments, the lipid nanoparticle formulations described herein may comprise a cationic lipid, a non-cationic lipid, a PEG lipid and a structural lipid. As a non-limiting example, the lipid nanoparticle comprise 50% of the cationic lipid DLin-KC2-DMA, 10% of the non-cationic lipid DSPC, 1.5% of the PEG lipid PEG-DOMG and 38.5% of the structural lipid cholesterol. As a non-limiting example, the lipid nanoparticle comprise 50% of the cationic lipid DLin-MC3-DMA, 10% of the non-cationic lipid DSPC, 1.5% of the PEG lipid PEG-DOMG and 38.5% of the structural lipid cholesterol. As a non-limiting example, the lipid nanoparticle comprise 50% of the cationic lipid DLin-MC3-DMA, 10% of the non-cationic lipid DSPC, 1.5% of the PEG lipid PEG-DMG and 38.5% of the structural lipid cholesterol. As yet another non-limiting example, the lipid nanoparticle comprise 55% of the cationic lipid L319, 10% of the non-cationic lipid DSPC, 2.5% of the PEG lipid PEG-DMG and 32.5% of the structural lipid cholesterol.

Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a vaccine composition may vary, depending upon the identity, size, and/or condition of the subject being treated and further depending upon the route by which the composition is to be administered. For example, the composition may comprise between 0.1% and 99% (w/w) of the active ingredient. By way of example, the composition may comprise between 0.1% and 100%, e.g., between 0.5 and 50%, between 1-30%, between 5-80%, at least 80% (w/w) active ingredient.

In some embodiments, the respiratory virus RNA (e.g. mRNA) vaccine composition may comprise the polynucleotide described herein, formulated in a lipid nanoparticle comprising MC3, Cholesterol, DSPC and PEG2000-DMG, the buffer trisodium citrate, sucrose and water for injection. As a non-limiting example, the composition comprises: 2.0 mg/mL of drug substance (e.g., polynucleotides encoding H10N8 hMPV), 21.8 mg/mL of MC3, 10.1 mg/mL of cholesterol, 5.4 mg/mL of DSPC, 2.7 mg/mL of PEG2000-DMG, 5.16 mg/mL of trisodium citrate, 71 mg/mL of sucrose and 1.0 mL of water for injection.

In some embodiments, a nanoparticle (e.g., a lipid nanoparticle) has a mean diameter of 10-500 nm, 20-400 nm, 30-300 nm, 40-200 nm. In some embodiments, a nanoparticle (e.g., a lipid nanoparticle) has a mean diameter of 50-150 nm, 50-200 nm, 80-100 nm or 80-200 nm.

Liposomes, Lipoplexes, and Lipid Nanoparticles

The RNA (e.g., mRNA) vaccines of the disclosure can be formulated using one or more liposomes, lipoplexes, or lipid nanoparticles. In some embodiments, pharmaceutical compositions of RNA (e.g., mRNA) vaccines include liposomes. Liposomes are artificially-prepared vesicles which may primarily be composed of a lipid bilayer and may be used as a delivery vehicle for the administration of nutrients and pharmaceutical formulations. Liposomes can be of different sizes such as, but not limited to, a multilamellar vesicle (MLV) which may be hundreds of nanometers in diameter and may contain a series of concentric bilayers separated by narrow aqueous compartments, a small unicellular vesicle (SUV) which may be smaller than 50 nm in diameter, and a large unilamellar vesicle (LUV) which may be between 50 and 500 nm in diameter. Liposome design may include, but is not limited to, opsonins or ligands in order to improve the attachment of liposomes to unhealthy tissue or to activate events such as, but not limited to, endocytosis. Liposomes may contain a low or a high pH in order to improve the delivery of the pharmaceutical formulations.

The formation of liposomes may depend on the physicochemical characteristics such as, but not limited to, the pharmaceutical formulation entrapped and the liposomal ingredients, the nature of the medium in which the lipid vesicles are dispersed, the effective concentration of the entrapped substance and its potential toxicity, any additional processes involved during the application and/or delivery of the vesicles, the optimization size, polydispersity and the shelf-life of the vesicles for the intended application, and the batch-to-batch reproducibility and possibility of large-scale production of safe and efficient liposomal products.

In some embodiments, pharmaceutical compositions described herein may include, without limitation, liposomes such as those formed from 1,2-dioleyloxy-N,N-dimethylaminopropane (DODMA) liposomes, DiLa2 liposomes from

Marina Biotech (Bothell, Wash.), 1,2-dilinoleyloxy-3-dimethylaminopropane (DLin-DMA), 2,2-dilinoleyl-4-(2-dimethylaminoethyl)-[1,3]-dioxolane (DLin-KC2-DMA), and MC3 (US20100324120; herein incorporated by reference in its entirety) and liposomes which may deliver small molecule drugs such as, but not limited to, DOXIL® from Janssen Biotech, Inc. (Horsham, Pa.).

In some embodiments, pharmaceutical compositions described herein may include, without limitation, liposomes such as those formed from the synthesis of stabilized plasmid-lipid particles (SPLP) or stabilized nucleic acid lipid particle (SNALP) that have been previously described and shown to be suitable for oligonucleotide delivery in vitro and in vivo (see Wheeler et al. Gene Therapy. 1999 6:271-281; Zhang et al. Gene Therapy. 1999 6:1438-1447; Jeffs et al. Pharm Res. 2005 22:362-372; Morrissey et al., Nat Biotechnol. 2005 2:1002-1007; Zimmermann et al., Nature. 2006 441:111-114; Heyes et al. J Contr Rel. 2005 107:276-287; Semple et al. Nature Biotech. 2010 28:172-176; Judge et al. J Clin Invest. 2009 119:661-673; deFougerolles Hum Gene Ther. 2008 19:125-132; U.S. Patent Publication No US20130122104; all of which are incorporated herein in their entireties). The original manufacture method by Wheeler et al. was a detergent dialysis method, which was later improved by Jeffs et al. and is referred to as the spontaneous vesicle formation method. The liposome formulations are composed of 3 to 4 lipid components in addition to the polynucleotide. As an example a liposome can contain, but is not limited to, 55% cholesterol, 20% disteroylphosphatidyl choline (DSPC), 10% PEG-S-DSG, and 15% 1,2-dioleyloxy-N,N-dimethylaminopropane (DODMA), as described by Jeffs et al. As another example, certain liposome formulations may contain, but are not limited to, 48% cholesterol, 20% DSPC, 2% PEG-c-DMA, and 30% cationic lipid, where the cationic lipid can be 1,2-distearloxy-N,N-dimethylaminopropane (DSDMA), DODMA, DLin-DMA, or 1,2-dilinolenyloxy-3-dimethylaminopropane (DLenDMA), as described by Heyes et al.

In some embodiments, liposome formulations may comprise from about 25.0% cholesterol to about 40.0% cholesterol, from about 30.0% cholesterol to about 45.0% cholesterol, from about 35.0% cholesterol to about 50.0% cholesterol and/or from about 48.5% cholesterol to about 60% cholesterol. In some embodiments, formulations may comprise a percentage of cholesterol selected from the group consisting of 28.5%, 31.5%, 33.5%, 36.5%, 37.0%, 38.5%, 39.0% and 43.5%. In some embodiments, formulations may comprise from about 5.0% to about 10.0% DSPC and/or from about 7.0% to about 15.0% DSPC.

In some embodiments, the RNA (e.g., mRNA) vaccine pharmaceutical compositions may be formulated in liposomes such as, but not limited to, DiLa2 liposomes (Marina Biotech, Bothell, Wash.), SMARTICLES® (Marina Biotech, Bothell, Wash.), neutral DOPC (1,2-dioleoyl-sn-glycero-3-phosphocholine) based liposomes (e.g., siRNA delivery for ovarian cancer (Landen et al. Cancer Biology & Therapy 2006 5(12)1708-1713); herein incorporated by reference in its entirety) and hyaluronan-coated liposomes (Quiet Therapeutics, Israel).

In some embodiments, the cationic lipid may be a low molecular weight cationic lipid such as those described in U.S. Patent Application No. 20130090372, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the RNA (e.g., mRNA) vaccines may be formulated in a lipid vesicle, which may have crosslinks between functionalized lipid bilayers.

In some embodiments, the RNA (e.g., mRNA) vaccines may be formulated in a lipid-polycation complex. The formation of the lipid-polycation complex may be accomplished by methods known in the art and/or as described in U.S. Pub. No. 20120178702, herein incorporated by reference in its entirety. As a non-limiting example, the polycation may include a cationic peptide or a polypeptide such as, but not limited to, polylysine, polyornithine and/or polyarginine. In some embodiments, the RNA (e.g., mRNA) vaccines may be formulated in a lipid-polycation complex, which may further include a non-cationic lipid such as, but not limited to, cholesterol or dioleoyl phosphatidylethanolamine (DOPE).

In some embodiments, the ratio of PEG in the lipid nanoparticle (LNP) formulations may be increased or decreased and/or the carbon chain length of the PEG lipid may be modified from C14 to C18 to alter the pharmacokinetics and/or biodistribution of the LNP formulations. As a non-limiting example, LNP formulations may contain from about 0.5% to about 3.0%, from about 1.0% to about 3.5%, from about 1.5% to about 4.0%, from about 2.0% to about 4.5%, from about 2.5% to about 5.0% and/or from about 3.0% to about 6.0% of the lipid molar ratio of PEG-c-DOMG (R-3-[(ω-methoxy-poly(ethyleneglycol)2000)carbamoyl)]-1,2-dimyristyloxypropyl-3-amine) (also referred to herein as PEG-DOMG) as compared to the cationic lipid, DSPC and cholesterol. In some embodiments, the PEG-c-DOMG may be replaced with a PEG lipid such as, but not limited to, PEG-DSG (1,2-Distearoyl-sn-glycerol, methoxypolyethylene glycol), PEG-DMG (1,2-Dimyristoyl-sn-glycerol) and/or PEG-DPG (1,2-Dipalmitoyl-sn-glycerol, methoxypolyethylene glycol). The cationic lipid may be selected from any lipid known in the art such as, but not limited to, DLin-MC3-DMA, DLin-DMA, C12-200 and DLin-KC2-DMA.

In some embodiments, the RNA (e.g., mRNA) vaccines may be formulated in a lipid nanoparticle.

In some embodiments, the RNA (e.g., mRNA) vaccine formulation comprising the polynucleotide is a nanoparticle which may comprise at least one lipid. The lipid may be selected from, but is not limited to, DLin-DMA, DLin-K-DMA, 98N12-5, C12-200, DLin-MC3-DMA, DLin-KC2-DMA, DODMA, PLGA, PEG, PEG-DMG, PEGylated lipids and amino alcohol lipids. In another aspect, the lipid may be a cationic lipid such as, but not limited to, DLin-DMA, DLin-D-DMA, DLin-MC3-DMA, DLin-KC2-DMA, DODMA and amino alcohol lipids. The amino alcohol cationic lipid may be the lipids described in and/or made by the methods described in U.S. Patent Publication No. US20130150625, herein incorporated by reference in its entirety. As a non-limiting example, the cationic lipid may be 2-amino-3-[(9Z, 12Z)-octadeca-9,12-dien-1-yloxy]-2-{[(9Z,2Z)-octadeca-9,12-dien-1-yloxy]methyl}propan-1-ol (Compound 1 in US20130150625); 2-amino-3-[(9Z)-octadec-9-en-1-yloxy]-2-{[(9Z)-octadec-9-en-1-yloxy]methyl}propan-1-ol (Compound 2 in US20130150625); 2-amino-3-[(9Z, 12Z)-octadeca-9,12-dien-1-yloxy]-2-[(octyloxy)methyl]propan-1-ol (Compound 3 in US20130150625); and 2-(dimethylamino)-3-[(9Z, 12Z)-octadeca-9,12-dien-1-yloxy]-2-{[(9Z, 12Z)-octadeca-9,12-dien-1-yloxy]methyl}propan-1-ol (Compound 4 in US20130150625); or any pharmaceutically acceptable salt or stereoisomer thereof.

Lipid nanoparticle formulations typically comprise a lipid, in particular, an ionizable cationic lipid, for example, 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobu-

tyrate (DLin-MC3-DMA), or di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), and further comprise a neutral lipid, a sterol and a molecule capable of reducing particle aggregation, for example a PEG or PEG-modified lipid.

In some embodiments, the lipid nanoparticle formulation consists essentially of (i) at least one lipid selected from the group consisting of 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy) heptadecanedioate (L319); (ii) a neutral lipid selected from DSPC, DPPC, POPC, DOPE and SM; (iii) a sterol, e.g., cholesterol; and (iv) a PEG-lipid, e.g., PEG-DMG or PEG-cDMA, in a molar ratio of about 20-60% cationic lipid: 5-25% neutral lipid: 25-55% sterol; 0.5-15% PEG-lipid.

In some embodiments, the formulation includes from about 25% to about 75% on a molar basis of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), e.g., from about 35 to about 65%, from about 45 to about 65%, about 60%, about 57.5%, about 50% or about 40% on a molar basis.

In some embodiments, the formulation includes from about 0.5% to about 15% on a molar basis of the neutral lipid e.g., from about 3 to about 12%, from about 5 to about 10% or about 15%, about 10%, or about 7.5% on a molar basis. Examples of neutral lipids include, but are not limited to, DSPC, POPC, DPPC, DOPE and SM. In some embodiments, the formulation includes from about 5% to about 50% on a molar basis of the sterol (e.g., about 15 to about 45%, about 20 to about 40%, about 40%, about 38.5%, about 35%, or about 31% on a molar basis. An exemplary sterol is cholesterol. In some embodiments, the formulation includes from about 0.5% to about 20% on a molar basis of the PEG or PEG-modified lipid (e.g., about 0.5 to about 10%, about 0.5 to about 5%, about 1.5%, about 0.5%, about 1.5%, about 3.5%, or about 5% on a molar basis. In some embodiments, the PEG or PEG modified lipid comprises a PEG molecule of an average molecular weight of 2,000 Da. In other embodiments, the PEG or PEG modified lipid comprises a PEG molecule of an average molecular weight of less than 2,000, for example around 1,500 Da, around 1,000 Da, or around 500 Da. Examples of PEG-modified lipids include, but are not limited to, PEG-distearoyl glycerol (PEG-DMG) (also referred herein as PEG-C14 or C14-PEG), PEG-cDMA (further discussed in Reyes et al. *J. Controlled Release,* 107, 276-287 (2005) the contents of which are herein incorporated by reference in their entirety)

In some embodiments, the formulations of the present disclosure include 25-75% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 0.5-15% of the neutral lipid, 5-50% of the sterol, and 0.5-20% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include 35-65% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 3-12% of the neutral lipid, 15-45% of the sterol, and 0.5-10% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include 45-65% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 5-10% of the neutral lipid, 25-40% of the sterol, and 0.5-10% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include about 60% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 7.5% of the neutral lipid, about 31% of the sterol, and about 1.5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include about 50% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 10% of the neutral lipid, about 38.5% of the sterol, and about 1.5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include about 50% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 10% of the neutral lipid, about 35% of the sterol, about 4.5% or about 5% of the PEG or PEG-modified lipid, and about 0.5% of the targeting lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include about 40% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 15% of the neutral lipid, about 40% of the sterol, and about 5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include about 57.2% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 7.1% of the neutral lipid, about 34.3% of the sterol, and about 1.4% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include about 57.5% of a cationic lipid selected from the PEG lipid is PEG-cDMA (PEG-cDMA is further discussed in Reyes et al. (*J. Controlled Release,* 107, 276-287 (2005), the contents of which are herein incorporated by reference in their entirety), about 7.5% of the neutral lipid, about 31.5% of the sterol, and about 3.5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulation consists essentially of a lipid mixture in molar ratios of about 20-70% cationic lipid: 5-45% neutral lipid: 20-55% cholesterol: 0.5-15% PEG-modified lipid; more preferably in a molar ratio of about 20-60% cationic lipid: 5-25% neutral lipid: 25-55% cholesterol: 0.5-15% PEG-modified lipid.

In some embodiments, the molar lipid ratio is approximately 50/10/38.5/1.5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG, PEG-DSG or PEG-DPG), 57.2/7.1134.3/1.4 (mol % cationic lipid/neutral lipid, e.g., DPPC/Chol/PEG-modified lipid, e.g., PEG-cDMA), 40/15/40/5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG), 50/10/35/4.5/0.5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DSG), 50/10/35/5 (cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG), 40/10/40/10 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG or PEG-cDMA), 35/15/40/10 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG or PEG-cDMA) or 52/13/30/5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG or PEG-cDMA).

Examples of lipid nanoparticle compositions and methods of making same are described, for example, in Semple et al. (2010) *Nat. Biotechnol.* 28:172-176; Jayarama et al. (2012), *Angew. Chem. Int. Ed.,* 51: 8529-8533; and Maier et al. (2013) *Molecular Therapy* 21, 1570-1578 (the contents of each of which are incorporated herein by reference in their entirety).

In some embodiments, the lipid nanoparticle formulations described herein may comprise a cationic lipid, a PEG lipid and a structural lipid and optionally comprise a non-cationic lipid. As a non-limiting example, the lipid nanoparticle may comprise about 40-60% of cationic lipid, about 5-15% of a non-cationic lipid, about 1-2% of a PEG lipid and about 30-50% of a structural lipid. As another non-limiting example, the lipid nanoparticle may comprise about 50% cationic lipid, about 10% non-cationic lipid, about 1.5% PEG lipid and about 38.5% structural lipid. As yet another non-limiting example, the lipid nanoparticle may comprise about 55% cationic lipid, about 10% non-cationic lipid, about 2.5% PEG lipid and about 32.5% structural lipid. In some embodiments, the cationic lipid may be any cationic lipid described herein such as, but not limited to, DLin-KC2-DMA, DLin-MC3-DMA and L319.

In some embodiments, the lipid nanoparticle formulations described herein may be 4 component lipid nanoparticles. The lipid nanoparticle may comprise a cationic lipid, a non-cationic lipid, a PEG lipid and a structural lipid. As a non-limiting example, the lipid nanoparticle may comprise about 40-60% of cationic lipid, about 5-15% of a non-cationic lipid, about 1-2% of a PEG lipid and about 30-50% of a structural lipid. As another non-limiting example, the lipid nanoparticle may comprise about 50% cationic lipid, about 10% non-cationic lipid, about 1.5% PEG lipid and about 38.5% structural lipid. As yet another non-limiting example, the lipid nanoparticle may comprise about 55% cationic lipid, about 10% non-cationic lipid, about 2.5% PEG lipid and about 32.5% structural lipid. In some embodiments, the cationic lipid may be any cationic lipid described herein such as, but not limited to, DLin-KC2-DMA, DLin-MC3-DMA and L319.

In some embodiments, the lipid nanoparticle formulations described herein may comprise a cationic lipid, a non-cationic lipid, a PEG lipid and a structural lipid. As a non-limiting example, the lipid nanoparticle comprise about 50% of the cationic lipid DLin-KC2-DMA, about 10% of the non-cationic lipid DSPC, about 1.5% of the PEG lipid PEG-DOMG and about 38.5% of the structural lipid cholesterol. As a non-limiting example, the lipid nanoparticle comprise about 50% of the cationic lipid DLin-MC3-DMA, about 10% of the non-cationic lipid DSPC, about 1.5% of the PEG lipid PEG-DOMG and about 38.5% of the structural lipid cholesterol. As a non-limiting example, the lipid nanoparticle comprise about 50% of the cationic lipid DLin-MC3-DMA, about 10% of the non-cationic lipid DSPC, about 1.5% of the PEG lipid PEG-DMG and about 38.5% of the structural lipid cholesterol. As yet another non-limiting example, the lipid nanoparticle comprise about 55% of the cationic lipid L319, about 10% of the non-cationic lipid DSPC, about 2.5% of the PEG lipid PEG-DMG and about 32.5% of the structural lipid cholesterol.

As a non-limiting example, the cationic lipid may be selected from (20Z,23Z)-N,N-dimethylnonacosa-20,23-dien-10-amine, (17Z,20Z)-N,N-dimemylhexacosa-17,20-dien-9-amine, (1Z,19Z)-N5N-dimethylpentacosa-16,19-dien-8-amine, (13Z,16Z)-N,N-dimethyldocosa-13,16-dien-5-amine, (12Z, 15Z)-N,N-dimethylhenicosa-12,15-dien-4-amine, (14Z, 17Z)-N,N-dimethyltricosa-14,17-dien-6-amine, (15Z, 18Z)-N,N-dimethyltetracosa-15,18-dien-7-amine, (18Z,21Z)-N,N-dimethylheptacosa-18,21-dien-10-amine, (15Z, 18Z)-N,N-dimethyltetracosa-15,18-dien-5-amine, (14Z, 17Z)-N,N-dimethyltricosa-14,17-dien-4-amine, (19Z,22Z)-N,N-dimeihyloctacosa-19,22-dien-9-amine, (18Z,21 Z)-N,N-dimethylheptacosa-18,21-dien-8-amine, (17Z,20Z)-N,N-dimethylhexacosa-17,20-dien-7-amine, (16Z, 19Z)-N,N-dimethylpentacosa-16,19-dien-6-amine, (22Z,25Z)-N,N-dimethylhentriaconta-22,25-dien-10-amine, (21 Z,24Z)-N,N-dimethyltriaconta-21,24-dien-9-amine, (18Z)-N,N-dimetylheptacos-18-en-10-amine, (17Z)-N,N-dimethylhexacos-17-en-9-amine, (19Z,22Z)-N,N-dimethyloctacosa-19,22-dien-7-amine, N,N-dimethylheptacosan-10-amine, (20Z,23Z)-N-ethyl-N-methylnonacosa-20,23-dien-10-amine, 1-[(11Z,14Z)-1-nonylicosa-11,14-dien-1-yl] pyrrolidine, (20Z)-N,N-dimethylheptacos-20-en-10-amine, (15Z)-N,N-dimethyl eptacos-15-en-10-amine, (14Z)-N,N-dimethylnonacos-14-en-10-amine, (17Z)-N,N-dimethylnonacos-17-en-10-amine, (24Z)-N,N-dimethyltritriacont-24-en-10-amine, (20Z)-N,N-dimethylnonacos-20-en-10-amine, (22Z)-N,N-dimethylhentriacont-22-en-10-amine, (16Z)-N,N-dimethylpentacos-16-en-8-amine, (12Z, 15Z)-N,N-dimethyl-2-nonylhenicosa-12,15-dien-1-amine, (13Z, 16Z)-N,N-dimethyl-3-nonyldocosa-13,16-dien-1-amine, N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl] eptadecan-8-amine, 1-[(1S,2R)-2-hexylcyclopropyl]-N,N-dimethylnonadecan-10-amine, N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]nonadecan-10-amine, N,N-dimethyl-21-[(1S,2R)-2-octylcyclopropyl] henicosan-10-amine,N,N-dimethyl-1-[(1S,2S)-2-{[(1R,2R)-2-pentylcyclopropyl]methyl}cyclopropyl]nonadecan-10-amine,N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl] hexadecan-8-amine, N,N-dimethyl-[(1R,2S)-2-undecylcyclopropyl]tetradecan-5-amine, N,N-dimethyl-3-{7-[(1S,2R)-2-octylcyclopropyl]heptyl} dodecan-1-amine, 1-[(1R,2S)-2-heptylcyclopropyl]-N,N-dimethyloctadecan-9-amine, 1-[(1S,2R)-2-decylcyclopropyl]-N,N-dimethyl-pentadecan-6-amine, N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]pentadecan-8-amine, R-N,N-dimethyl-1-[(9Z, 12Z)-octadeca-9,12-dien-1-yloxy]-3-(octyloxy)propan-2-amine, S-N,N-dimethyl-1-[(9Z, 12Z)-octadeca-9,12-dien-1-yloxy]-3-(octyloxy)propan-2-amine, 1-{2-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-1-[(octyloxy)methyl] ethyl}pyrrolidine, (2S)-N,N-dimethyl-1-[(9Z, 12Z)-octadeca-9,12-dien-1-yloxy]-3-[(5Z)-oct-5-en-1-yloxy] propan-2-amine, 1-{2-[(9Z, 12Z)-octadeca-9,12-dien-1-yloxy]-1-[(octyloxy)methyl]ethyl}azetidine, (2S)-1-(hexyloxy)-N,N-dimethyl-3-[(9Z, 12Z)-octadeca-9,12-dien-1-yloxy]propan-2-amine, (2S)-1-(heptyloxy)-N,N-dimethyl-3-[(9Z, 12Z)-octadeca-9,12-dien-1-yloxy]propan-

2-amine, N,N-dimethyl-1-(nonyloxy)-3-[(9Z, 12Z)-octadeca-9,12-dien-1-yloxy]propan-2-amine, N,N-dimethyl-1-[(9Z)-octadec-9-en-1-yloxy]-3-(octyloxy) propan-2-amine; (2S)-N,N-dimethyl-1-[(6Z,9Z, 12Z)-octadeca-6,9,12-trien-1-yloxy]-3-(octyloxy)propan-2-amine, (2S)-1-[(11Z,14Z)-icosa-11,14-dien-1-yloxy]-N,N-dimethyl-3-(pentyloxy)propan-2-amine, (2S)-1-(hexyloxy)-3-[(11Z,14Z)-icosa-11,14-dien-1-yloxy]-N,N-dimethylpropan-2-amine, 1-[(11Z,14Z)-icosa-11,14-dien-1-yloxy]-N,N-dimethyl-3-(octyloxy)propan-2-amine, 1-[(13Z, 16Z)-docosa-13,16-dien-1-yloxy]-N,N-dimethyl-3-(octyloxy)propan-2-amine, (2S)-1-[(13Z,16Z)-docosa-13, 16-dien-1-yloxy]-3-(hexyloxy)-N,N-dimethylpropan-2-amine, (2S)-1-[(13Z)-docos-13-en-1-yloxy]-3-(hexyloxy)-N,N-dimethylpropan-2-amine, 1-[(13Z)-docos-13-en-1-yloxy]-N,N-dimethyl-3-(octyloxy)propan-2-amine, 1-[(9Z)-hexadec-9-en-1-yloxy]-N,N-dimethyl-3-(octyloxy)propan-2-amine, (2R)-N,N-dimethyl-H(1-metoylo ctyl)oxy]-3-[(9Z, 12Z)-octadeca-9,12-dien-1-yloxy]propan-2-amine, (2R)-1-[(3,7-dimethyloctyl)oxy]-N,N-dimethyl-3-[(9Z, 12Z)-octadeca-9,12-dien-1-yloxy]propan-2-amine, N,N-dimethyl-1-(octyloxy)-3-({8-[(1S,2S)-2-{[(1R,2R)-2-pentylcyclopropyl]methyl}cyclopropyl]octyl}oxy)propan-2-amine, N,N-dimethyl-1-{[8-(2-oc1ylcyclopropyl)octyl] oxy}-3-(octyloxy)propan-2-amine and (11E,20Z,23Z)-N,N-dimethylnonacosa-11,20,2-trien-10-amine or a pharmaceutically acceptable salt or stereoisomer thereof.

In some embodiments, the LNP formulations of the RNA (e.g., mRNA) vaccines may contain PEG-c-DOMG at 3% lipid molar ratio. In some embodiments, the LNP formulations of the RNA (e.g., mRNA) vaccines may contain PEG-c-DOMG at 1.5% lipid molar ratio.

In some embodiments, the pharmaceutical compositions of the RNA (e.g., mRNA) vaccines may include at least one of the PEGylated lipids described in International Publication No. WO2012099755, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the LNP formulation may contain PEG-DMG 2000 (1,2-dimyristoyl-sn-glycero-3-phophoethanolamine-N-[methoxy(polyethylene glycol)-2000). In some embodiments, the LNP formulation may contain PEG-DMG 2000, a cationic lipid known in the art and at least one other component. In some embodiments, the LNP formulation may contain PEG-DMG 2000, a cationic lipid known in the art, DSPC and cholesterol. As a non-limiting example, the LNP formulation may contain PEG-DMG 2000, DLin-DMA, DSPC and cholesterol. As another non-limiting example the LNP formulation may contain PEG-DMG 2000, DLin-DMA, DSPC and cholesterol in a molar ratio of 2:40:10:48 (see e.g., Geall et al., Nonviral delivery of self-amplifying RNA (e.g., mRNA) vaccines, PNAS 2012; PMID: 22908294, the contents of each of which are herein incorporated by reference in their entirety).

The lipid nanoparticles described herein may be made in a sterile environment.

In some embodiments, the LNP formulation may be formulated in a nanoparticle such as a nucleic acid-lipid particle. As a non-limiting example, the lipid particle may comprise one or more active agents or therapeutic agents; one or more cationic lipids comprising from about 50 mol % to about 85 mol % of the total lipid present in the particle; one or more non-cationic lipids comprising from about 13 mol % to about 49.5 mol % of the total lipid present in the particle; and one or more conjugated lipids that inhibit aggregation of particles comprising from about 0.5 mol % to about 2 mol % of the total lipid present in the particle.

The nanoparticle formulations may comprise a phosphate conjugate. The phosphate conjugate may increase in vivo circulation times and/or increase the targeted delivery of the nanoparticle. As a non-limiting example, the phosphate conjugates may include a compound of any one of the formulas described in International Application No. WO2013033438, the contents of which are herein incorporated by reference in its entirety.

The nanoparticle formulation may comprise a polymer conjugate. The polymer conjugate may be a water soluble conjugate. The polymer conjugate may have a structure as described in U.S. Patent Application No. 20130059360, the contents of which are herein incorporated by reference in its entirety. In some embodiments, polymer conjugates with the polynucleotides of the present disclosure may be made using the methods and/or segmented polymeric reagents described in U.S. Patent Application No. 20130072709, the contents of which are herein incorporated by reference in its entirety. In some embodiments, the polymer conjugate may have pendant side groups comprising ring moieties such as, but not limited to, the polymer conjugates described in U.S. Patent Publication No. US20130196948, the contents which are herein incorporated by reference in its entirety.

The nanoparticle formulations may comprise a conjugate to enhance the delivery of nanoparticles of the present disclosure in a subject. Further, the conjugate may inhibit phagocytic clearance of the nanoparticles in a subject. In one aspect, the conjugate may be a "self" peptide designed from the human membrane protein CD47 (e.g., the "self" particles described by Rodriguez et al. (*Science* 2013 339, 971-975), herein incorporated by reference in its entirety). As shown by Rodriguez et al., the self peptides delayed macrophage-mediated clearance of nanoparticles which enhanced delivery of the nanoparticles. In another aspect, the conjugate may be the membrane protein CD47 (e.g., see Rodriguez et al. *Science* 2013 339, 971-975, herein incorporated by reference in its entirety). Rodriguez et al. showed that, similarly to "self" peptides, CD47 can increase the circulating particle ratio in a subject as compared to scrambled peptides and PEG coated nanoparticles.

In some embodiments, the RNA (e.g., mRNA) vaccines of the present disclosure are formulated in nanoparticles which comprise a conjugate to enhance the delivery of the nanoparticles of the present disclosure in a subject. The conjugate may be the CD47 membrane or the conjugate may be derived from the CD47 membrane protein, such as the "self" peptide described previously. In some embodiments, the nanoparticle may comprise PEG and a conjugate of CD47 or a derivative thereof. In some embodiments, the nanoparticle may comprise both the "self" peptide described above and the membrane protein CD47.

In some embodiments, a "self" peptide and/or CD47 protein may be conjugated to a virus-like particle or pseudovirion, as described herein for delivery of the RNA (e.g., mRNA) vaccines of the present disclosure.

In some embodiments, RNA (e.g., mRNA) vaccine pharmaceutical compositions comprising the polynucleotides of the present disclosure and a conjugate that may have a degradable linkage. Non-limiting examples of conjugates include an aromatic moiety comprising an ionizable hydrogen atom, a spacer moiety, and a water-soluble polymer. As a non-limiting example, pharmaceutical compositions comprising a conjugate with a degradable linkage and methods for delivering such pharmaceutical compositions are described in U.S. Patent Publication No. US20130184443, the contents of which are herein incorporated by reference in their entirety.

The nanoparticle formulations may be a carbohydrate nanoparticle comprising a carbohydrate carrier and a RNA (e.g., mRNA) vaccine. As a non-limiting example, the carbohydrate carrier may include, but is not limited to, an anhydride-modified phytoglycogen or glycogen-type material, phtoglycogen octenyl succinate, phytoglycogen beta-dextrin, anhydride-modified phytoglycogen beta-dextrin. (See e.g., International Publication No. WO2012109121; the contents of which are herein incorporated by reference in their entirety).

Nanoparticle formulations of the present disclosure may be coated with a surfactant or polymer in order to improve the delivery of the particle. In some embodiments, the nanoparticle may be coated with a hydrophilic coating such as, but not limited to, PEG coatings and/or coatings that have a neutral surface charge. The hydrophilic coatings may help to deliver nanoparticles with larger payloads such as, but not limited to, RNA (e.g., mRNA) vaccines within the central nervous system. As a non-limiting example nanoparticles comprising a hydrophilic coating and methods of making such nanoparticles are described in U.S. Patent Publication No. US20130183244, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the lipid nanoparticles of the present disclosure may be hydrophilic polymer particles. Non-limiting examples of hydrophilic polymer particles and methods of making hydrophilic polymer particles are described in U.S. Patent Publication No. US20130210991, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the lipid nanoparticles of the present disclosure may be hydrophobic polymer particles.

Lipid nanoparticle formulations may be improved by replacing the cationic lipid with a biodegradable cationic lipid which is known as a rapidly eliminated lipid nanoparticle (reLNP). Ionizable cationic lipids, such as, but not limited to, DLinDMA, DLin-KC2-DMA, and DLin-MC3-DMA, have been shown to accumulate in plasma and tissues over time and may be a potential source of toxicity. The rapid metabolism of the rapidly eliminated lipids can improve the tolerability and therapeutic index of the lipid nanoparticles by an order of magnitude from a 1 mg/kg dose to a 10 mg/kg dose in rat. Inclusion of an enzymatically degraded ester linkage can improve the degradation and metabolism profile of the cationic component, while still maintaining the activity of the reLNP formulation. The ester linkage can be internally located within the lipid chain or it may be terminally located at the terminal end of the lipid chain. The internal ester linkage may replace any carbon in the lipid chain.

In some embodiments, the internal ester linkage may be located on either side of the saturated carbon.

In some embodiments, an immune response may be elicited by delivering a lipid nanoparticle which may include a nanospecies, a polymer and an immunogen. (U.S. Publication No. 20120189700 and International Publication No. WO2012099805; each of which is herein incorporated by reference in their entirety). The polymer may encapsulate the nanospecies or partially encapsulate the nanospecies. The immunogen may be a recombinant protein, a modified RNA and/or a polynucleotide described herein. In some embodiments, the lipid nanoparticle may be formulated for use in a vaccine such as, but not limited to, against a pathogen.

Lipid nanoparticles may be engineered to alter the surface properties of particles so the lipid nanoparticles may penetrate the mucosal barrier. Mucus is located on mucosal tissue such as, but not limited to, oral (e.g., the buccal and esophageal membranes and tonsil tissue), ophthalmic, gastrointestinal (e.g., stomach, small intestine, large intestine, colon, rectum), nasal, respiratory (e.g., nasal, pharyngeal, tracheal and bronchial membranes), genital (e.g., vaginal, cervical and urethral membranes). Nanoparticles larger than 10-200 nm which are preferred for higher drug encapsulation efficiency and the ability to provide the sustained delivery of a wide array of drugs have been thought to be too large to rapidly diffuse through mucosal barriers. Mucus is continuously secreted, shed, discarded or digested and recycled so most of the trapped particles may be removed from the mucosa tissue within seconds or within a few hours. Large polymeric nanoparticles (200 nm-500 nm in diameter) which have been coated densely with a low molecular weight polyethylene glycol (PEG) diffused through mucus only 4 to 6-fold lower than the same particles diffusing in water (Lai et al. PNAS 2007 104(5):1482-487; Lai et al. *Adv Drug Deliv Rev.* 2009 61(2): 158-171; each of which is herein incorporated by reference in their entirety). The transport of nanoparticles may be determined using rates of permeation and/or fluorescent microscopy techniques including, but not limited to, fluorescence recovery after photobleaching (FRAP) and high resolution multiple particle tracking (MPT). As a non-limiting example, compositions which can penetrate a mucosal barrier may be made as described in U.S. Pat. No. 8,241,670 or International Patent Publication No. WO2013110028, the contents of each of which are herein incorporated by reference in its entirety.

The lipid nanoparticle engineered to penetrate mucus may comprise a polymeric material (i.e. a polymeric core) and/or a polymer-vitamin conjugate and/or a tri-block co-polymer. The polymeric material may include, but is not limited to, polyamines, polyethers, polyamides, polyesters, polycarbamates, polyureas, polycarbonates, poly(styrenes), polyimides, polysulfones, polyurethanes, polyacetylenes, polyethylenes, polyethyeneimines, polyisocyanates, polyacrylates, polymethacrylates, polyacrylonitriles, and polyarylates. The polymeric material may be biodegradable and/or biocompatible. Non-limiting examples of biocompatible polymers are described in International Patent Publication No. WO2013116804, the contents of which are herein incorporated by reference in their entirety. The polymeric material may additionally be irradiated. As a non-limiting example, the polymeric material may be gamma irradiated (see e.g., International App. No. WO201282165, herein incorporated by reference in its entirety). Non-limiting examples of specific polymers include poly(caprolactone) (PCL), ethylene vinyl acetate polymer (EVA), poly(lactic acid) (PLA), poly(L-lactic acid) (PLLA), poly(glycolic acid) (PGA), poly (lactic acid-co-glycolic acid) (PLGA), poly(L-lactic acid-co-glycolic acid) (PLLGA), poly(D,L-lactide) (PDLA), poly (L-lactide) (PLLA), poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-caprolactone-co-glycolide), poly(D,L-lactide-co-PEO-co-D,L-lactide), poly(D,L-lactide-co-PPO-co-D,L-lactide), polyalkyl cyanoacralate, polyurethane, poly-L-lysine (PLL), hydroxypropyl methacrylate (HPMA), polyethyleneglycol, poly-L-glutamic acid, poly(hydroxy acids), polyanhydrides, polyorthoesters, poly(ester amides), polyamides, poly(ester ethers), polycarbonates, polyalkylenes such as polyethylene and polypropylene, polyalkylene glycols such as poly(ethylene glycol) (PEG), polyalkylene oxides (PEO), polyalkylene terephthalates such as poly (ethylene terephthalate), polyvinyl alcohols (PVA), polyvinyl ethers, polyvinyl esters such as poly(vinyl acetate), polyvinyl halides such as poly(vinyl chloride) (PVC), poly-

vinylpyrrolidone, polysiloxanes, polystyrene (PS), polyurethanes, derivatized celluloses such as alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, hydroxypropylcellulose, carboxymethylcellulose, polymers of acrylic acids, such as poly(methyl(meth) acrylate) (PMMA), poly(ethyl(meth)acrylate), poly(butyl (meth)acrylate), poly(isobutyl(meth)acrylate), poly(hexyl (meth)acrylate), poly(isodecyl(meth)acrylate), poly(lauryl (meth)acrylate), poly(phenyl(meth)acrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate) and copolymers and mixtures thereof, polydioxanone and its copolymers, polyhydroxyalkanoates, polypropylene fumarate, polyoxymethylene, poloxamers, poly(ortho)esters, poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), PEG-PLGA-PEG and trimethylene carbonate, polyvinylpyrrolidone. The lipid nanoparticle may be coated or associated with a co-polymer such as, but not limited to, a block co-polymer (such as a branched polyether-polyamide block copolymer described in International Publication No. WO2013012476, herein incorporated by reference in its entirety), and (poly(ethylene glycol))-(poly(propylene oxide))-(poly(ethylene glycol)) triblock copolymer (see e.g., U.S. Publication 20120121718 and U.S. Publication 20100003337 and U.S. Pat. No. 8,263,665, the contents of each of which is herein incorporated by reference in their entirety). The co-polymer may be a polymer that is generally regarded as safe (GRAS) and the formation of the lipid nanoparticle may be in such a way that no new chemical entities are created. For example, the lipid nanoparticle may comprise poloxamers coating PLGA nanoparticles without forming new chemical entities which are still able to rapidly penetrate human mucus (Yang et al. Angew. Chem. Int. Ed. 2011 50:2597-2600; the contents of which are herein incorporated by reference in their entirety). A non-limiting scalable method to produce nanoparticles which can penetrate human mucus is described by Xu et al. (see, e.g., J Control Release 2013, 170(2):279-86; the contents of which are herein incorporated by reference in their entirety).

The vitamin of the polymer-vitamin conjugate may be vitamin E. The vitamin portion of the conjugate may be substituted with other suitable components such as, but not limited to, vitamin A, vitamin E, other vitamins, cholesterol, a hydrophobic moiety, or a hydrophobic component of other surfactants (e.g., sterol chains, fatty acids, hydrocarbon chains and alkylene oxide chains).

The lipid nanoparticle engineered to penetrate mucus may include surface altering agents such as, but not limited to, polynucleotides, anionic proteins (e.g., bovine serum albumin), surfactants (e.g., cationic surfactants such as for example dimethyldioctadecyl-ammonium bromide), sugars or sugar derivatives (e.g., cyclodextrin), nucleic acids, polymers (e.g., heparin, polyethylene glycol and poloxamer), mucolytic agents (e.g., N-acetylcysteine, mugwort, bromelain, papain, clerodendrum, acetylcysteine, bromhexine, carbocisteine, eprazinone, mesna, ambroxol, sobrerol, domiodol, letosteine, stepronin, tiopronin, gelsolin, thymosin 34 dornase alfa, neltenexine, erdosteine) and various DNases including rhDNase. The surface altering agent may be embedded or enmeshed in the particle's surface or disposed (e.g., by coating, adsorption, covalent linkage, or other process) on the surface of the lipid nanoparticle. (see e.g., U.S. Publication 20100215580 and U.S. Publication 20080166414 and US20130164343; the contents of each of which are herein incorporated by reference in their entirety).

In some embodiments, the mucus penetrating lipid nanoparticles may comprise at least one polynucleotide described herein. The polynucleotide may be encapsulated in the lipid nanoparticle and/or disposed on the surface of the particle. The polynucleotide may be covalently coupled to the lipid nanoparticle. Formulations of mucus penetrating lipid nanoparticles may comprise a plurality of nanoparticles. Further, the formulations may contain particles which may interact with the mucus and alter the structural and/or adhesive properties of the surrounding mucus to decrease mucoadhesion, which may increase the delivery of the mucus penetrating lipid nanoparticles to the mucosal tissue.

In some embodiments, the mucus penetrating lipid nanoparticles may be a hypotonic formulation comprising a mucosal penetration enhancing coating. The formulation may be hypotonice for the epithelium to which it is being delivered. Non-limiting examples of hypotonic formulations may be found in International Patent Publication No. WO2013110028, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, in order to enhance the delivery through the mucosal barrier the RNA (e.g., mRNA) vaccine formulation may comprise or be a hypotonic solution.

Hypotonic solutions were found to increase the rate at which mucoinert particles such as, but not limited to, mucus-penetrating particles, were able to reach the vaginal epithelial surface (see e.g., Ensign et al. Biomaterials 2013 34(28):6922-9, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the RNA (e.g., mRNA) vaccine is formulated as a lipoplex, such as, without limitation, the ATUPLEX™ system, the DACC system, the DBTC system and other siRNA-lipoplex technology from Silence Therapeutics (London, United Kingdom), STEMFECT™ from STEMGENT® (Cambridge, Mass.), and polyethylenimine (PEI) or protamine-based targeted and non-targeted delivery of nucleic acids acids (Aleku et al. Cancer Res. 2008 68:9788-9798; Strumberg et al. Int J Clin Pharmacol Ther 2012 50:76-78; Santel et al., Gene Ther 2006 13:1222-1234; Santel et al., Gene Ther 2006 13:1360-1370; Gutbier et al., Pulm Pharmacol. Ther. 2010 23:334-344; Kaufmann et al. Microvasc Res 2010 80:286-293Weide et al. J Immunother. 2009 32:498-507; Weide et al. J Immunother. 2008 31:180-188; Pascolo Expert Opin. Biol. Ther. 4:1285-1294; Fotin-Mleczek et al., 2011 J. Immunother. 34:1-15; Song et al., Nature Biotechnol. 2005, 23:709-717; Peer et al., Proc Natl Acad Sci USA. 2007 6; 104:4095-4100; deFougerolles Hum Gene Ther. 2008 19:125-132, the contents of each of which are incorporated herein by reference in their entirety).

In some embodiments, such formulations may also be constructed or compositions altered such that they passively or actively are directed to different cell types in vivo, including but not limited to hepatocytes, immune cells, tumor cells, endothelial cells, antigen presenting cells, and leukocytes (Akinc et al. Mol Ther. 2010 18:1357-1364; Song et al., Nat Biotechnol. 2005 23:709-717; Judge et al., J Clin Invest. 2009 119:661-673; Kaufmann et al., Microvasc Res 2010 80:286-293; Santel et al., Gene Ther 2006 13:1222-1234; Santel et al., Gene Ther 2006 13:1360-1370; Gutbier et al., Pulm Pharmacol. Ther. 2010 23:334-344; Basha et al., Mol. Ther. 2011 19:2186-2200; Fenske and Cullis, Expert Opin Drug Deliv. 2008 5:25-44; Peer et al., Science. 2008 319:627-630; Peer and Lieberman, Gene Ther. 2011 18:1127-1133, the contents of each of which are incorporated herein by reference in their entirety). One example of passive targeting of formulations to liver cells includes the DLin-DMA, DLin-KC2-DMA and DLin-MC3-DMA-based lipid nanoparticle formulations, which have been shown to bind to apolipoprotein E and promote binding

and uptake of these formulations into hepatocytes in vivo (Akinc et al. Mol Ther. 2010 18:1357-1364, the contents of which are incorporated herein by reference in their entirety). Formulations can also be selectively targeted through expression of different ligands on their surface as exemplified by, but not limited by, folate, transferrin, N-acetylgalactosamine (GalNAc), and antibody targeted approaches (Kolhatkar et al., Curr Drug Discov Technol. 2011 8:197-206; Musacchio and Torchilin, Front Biosci. 2011 16:1388-1412; Yu et al., Mol Membr Biol. 2010 27:286-298; Patil et al., Crit Rev Ther Drug Carrier Syst. 2008 25:1-61; Benoit et al., Biomacromolecules. 2011 12:2708-2714; Zhao et al., Expert Opin Drug Deliv. 2008 5:309-319; Akinc et al., Mol Ther. 2010 18:1357-1364; Srinivasan et al., Methods Mol Biol. 2012 820:105-116; Ben-Arie et al., Methods Mol Biol. 2012 757:497-507; Peer 2010 J Control Release. 20:63-68; Peer et al., Proc Natl Acad Sci USA. 2007 104:4095-4100; Kim et al., Methods Mol Biol. 2011 721:339-353; Subramanya et al., Mol Ther. 2010 18:2028-2037; Song et al., Nat Biotechnol. 2005 23:709-717; Peer et al., Science. 2008 319:627-630; Peer and Lieberman, Gene Ther. 2011 18:1127-1133, the contents of each of which are incorporated herein by reference in their entirety).

In some embodiments, the RNA (e.g., mRNA) vaccine is formulated as a solid lipid nanoparticle. A solid lipid nanoparticle (SLN) may be spherical with an average diameter between 10 to 1000 nm. SLN possess a solid lipid core matrix that can solubilize lipophilic molecules and may be stabilized with surfactants and/or emulsifiers. In some embodiments, the lipid nanoparticle may be a self-assembly lipid-polymer nanoparticle (see Zhang et al., ACS Nano, 2008, 2 (8), pp 1696-1702; the contents of which are herein incorporated by reference in their entirety). As a non-limiting example, the SLN may be the SLN described in International Patent Publication No. WO2013105101, the contents of which are herein incorporated by reference in their entirety. As another non-limiting example, the SLN may be made by the methods or processes described in International Patent Publication No. WO2013105101, the contents of which are herein incorporated by reference in their entirety.

Liposomes, lipoplexes, or lipid nanoparticles may be used to improve the efficacy of polynucleotides directed protein production as these formulations may be able to increase cell transfection by the RNA (e.g., mRNA) vaccine; and/or increase the translation of encoded protein. One such example involves the use of lipid encapsulation to enable the effective systemic delivery of polyplex plasmid DNA (Heyes et al., Mol Ther. 2007 15:713-720; the contents of which are incorporated herein by reference in their entirety). The liposomes, lipoplexes, or lipid nanoparticles may also be used to increase the stability of the polynucleotide.

In some embodiments, the RNA (e.g., mRNA) vaccines of the present disclosure can be formulated for controlled release and/or targeted delivery. As used herein, "controlled release" refers to a pharmaceutical composition or compound release profile that conforms to a particular pattern of release to effect a therapeutic outcome. In some embodiments, the RNA (e.g., mRNA) vaccines may be encapsulated into a delivery agent described herein and/or known in the art for controlled release and/or targeted delivery. As used herein, the term "encapsulate" means to enclose, surround or encase. As it relates to the formulation of the compounds of the disclosure, encapsulation may be substantial, complete or partial. The term "substantially encapsulated" means that at least greater than 50, 60, 70, 80, 85, 90, 95, 96, 97, 98, 99, 99.9, 99.9 or greater than 99.999% of the pharmaceutical composition or compound of the disclosure may be enclosed, surrounded or encased within the delivery agent. "Partially encapsulation" means that less than 10, 10, 20, 30, 40 50 or less of the pharmaceutical composition or compound of the disclosure may be enclosed, surrounded or encased within the delivery agent. Advantageously, encapsulation may be determined by measuring the escape or the activity of the pharmaceutical composition or compound of the disclosure using fluorescence and/or electron micrograph. For example, at least 1, 5, 10, 20, 30, 40, 50, 60, 70, 80, 85, 90, 95, 96, 97, 98, 99, 99.9, 99.99 or greater than 99.99% of the pharmaceutical composition or compound of the disclosure are encapsulated in the delivery agent.

In some embodiments, the controlled release formulation may include, but is not limited to, tri-block co-polymers. As a non-limiting example, the formulation may include two different types of tri-block co-polymers (International Pub. No. WO2012131104 and WO2012131106, the contents of each of which are incorporated herein by reference in their entirety).

In some embodiments, the RNA (e.g., mRNA) vaccines may be encapsulated into a lipid nanoparticle or a rapidly eliminated lipid nanoparticle and the lipid nanoparticles or a rapidly eliminated lipid nanoparticle may then be encapsulated into a polymer, hydrogel and/or surgical sealant described herein and/or known in the art. As a non-limiting example, the polymer, hydrogel or surgical sealant may be PLGA, ethylene vinyl acetate (EVAc), poloxamer, GELSITE® (Nanotherapeutics, Inc. Alachua, Fla.), HYLENEX® (Halozyme Therapeutics, San Diego Calif.), surgical sealants such as fibrinogen polymers (Ethicon Inc. Cornelia, Ga.), TISSELL® (Baxter International, Inc Deerfield, Ill.), PEG-based sealants, and COSEAL® (Baxter International, Inc Deerfield, Ill.).

In some embodiments, the lipid nanoparticle may be encapsulated into any polymer known in the art which may form a gel when injected into a subject. As another non-limiting example, the lipid nanoparticle may be encapsulated into a polymer matrix which may be biodegradable.

In some embodiments, the RNA (e.g., mRNA) vaccine formulation for controlled release and/or targeted delivery may also include at least one controlled release coating. Controlled release coatings include, but are not limited to, OPADRY®, polyvinylpyrrolidone/vinyl acetate copolymer, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, EUDRAGIT RL®, EUDRAGIT RS® and cellulose derivatives such as ethylcellulose aqueous dispersions (AQUACOAT® and SURELEASE®).

In some embodiments, the RNA (e.g., mRNA) vaccine controlled release and/or targeted delivery formulation may comprise at least one degradable polyester which may contain polycationic side chains. Degradeable polyesters include, but are not limited to, poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester), and combinations thereof. In some embodiments, the degradable polyesters may include a PEG conjugation to form a PEGylated polymer.

In some embodiments, the RNA (e.g., mRNA) vaccine controlled release and/or targeted delivery formulation comprising at least one polynucleotide may comprise at least one PEG and/or PEG related polymer derivatives as described in U.S. Pat. No. 8,404,222, the contents of which are incorporated herein by reference in their entirety.

In some embodiments, the RNA (e.g., mRNA) vaccine controlled release delivery formulation comprising at least one polynucleotide may be the controlled release polymer

system described in US20130130348, the contents of which are incorporated herein by reference in their entirety.

In some embodiments, the RNA (e.g., mRNA) vaccines of the present disclosure may be encapsulated in a therapeutic nanoparticle, referred to herein as "therapeutic nanoparticle RNA (e.g., mRNA) vaccines." Therapeutic nanoparticles may be formulated by methods described herein and known in the art such as, but not limited to, International Pub Nos. WO2010005740, WO2010030763, WO2010005721, WO2010005723, WO2012054923, U.S. Publication Nos. US20110262491, US20100104645, US20100087337, US20100068285, US20110274759, US20100068286, US20120288541, US20130123351 and US20130230567 and U.S. Pat. Nos. 8,206,747, 8,293,276, 8,318,208 and 8,318,211; the contents of each of which are herein incorporated by reference in their entirety. In some embodiments, therapeutic polymer nanoparticles may be identified by the methods described in US Pub No. US20120140790, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the therapeutic nanoparticle RNA (e.g., mRNA) vaccine may be formulated for sustained release. As used herein, "sustained release" refers to a pharmaceutical composition or compound that conforms to a release rate over a specific period of time. The period of time may include, but is not limited to, hours, days, weeks, months and years. As a non-limiting example, the sustained release nanoparticle may comprise a polymer and a therapeutic agent such as, but not limited to, the polynucleotides of the present disclosure (see International Pub No. 2010075072 and US Pub No. US20100216804, US20110217377 and US20120201859, the contents of each of which are incorporated herein by reference in their entirety). In another non-limiting example, the sustained release formulation may comprise agents which permit persistent bioavailability such as, but not limited to, crystals, macromolecular gels and/or particulate suspensions (see U.S. Patent Publication No US20130150295, the contents of each of which are incorporated herein by reference in their entirety).

In some embodiments, the therapeutic nanoparticle RNA (e.g., mRNA) vaccines may be formulated to be target specific. As a non-limiting example, the therapeutic nanoparticles may include a corticosteroid (see International Pub. No. WO2011084518, the contents of which are incorporated herein by reference in their entirety). As a non-limiting example, the therapeutic nanoparticles may be formulated in nanoparticles described in International Pub No. WO2008121949, WO2010005726, WO2010005725, WO2011084521 and US Pub No. US20100069426, US20120004293 and US20100104655, the contents of each of which are incorporated herein by reference in their entirety.

In some embodiments, the nanoparticles of the present disclosure may comprise a polymeric matrix. As a non-limiting example, the nanoparticle may comprise two or more polymers such as, but not limited to, polyethylenes, polycarbonates, polyanhydrides, polyhydroxyacids, polypropylfumerates, polycaprolactones, polyamides, polyacetals, polyethers, polyesters, poly(orthoesters), polycyanoacrylates, polyvinyl alcohols, polyurethanes, polyphosphazenes, polyacrylates, polymethacrylates, polycyanoacrylates, polyureas, polystyrenes, polyamines, polylysine, poly(ethylene imine), poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester) or combinations thereof.

In some embodiments, the therapeutic nanoparticle comprises a diblock copolymer. In some embodiments, the diblock copolymer may include PEG in combination with a polymer such as, but not limited to, polyethylenes, polycarbonates, polyanhydrides, polyhydroxyacids, polypropylfumerates, polycaprolactones, polyamides, polyacetals, polyethers, polyesters, poly(orthoesters), polycyanoacrylates, polyvinyl alcohols, polyurethanes, polyphosphazenes, polyacrylates, polymethacrylates, polycyanoacrylates, polyureas, polystyrenes, polyamines, polylysine, poly(ethylene imine), poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester) or combinations thereof. In yet another embodiment, the diblock copolymer may be a high-X diblock copolymer such as those described in International Patent Publication No. WO2013120052, the contents of which are incorporated herein by reference in their entirety.

As a non-limiting example the therapeutic nanoparticle comprises a PLGA-PEG block copolymer (see U.S. Publication No. US20120004293 and U.S. Pat. No. 8,236,330, each of which is herein incorporated by reference in their entirety). In another non-limiting example, the therapeutic nanoparticle is a stealth nanoparticle comprising a diblock copolymer of PEG and PLA or PEG and PLGA (see U.S. Pat. No. 8,246,968 and International Publication No. WO2012166923, the contents of each of which are herein incorporated by reference in their entirety). In yet another non-limiting example, the therapeutic nanoparticle is a stealth nanoparticle or a target-specific stealth nanoparticle as described in U.S. Patent Publication No. US20130172406, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the therapeutic nanoparticle may comprise a multiblock copolymer (see e.g., U.S. Pat. Nos. 8,263,665 and 8,287,910 and U.S. Patent Pub. No. US20130195987, the contents of each of which are herein incorporated by reference in their entirety).

In yet another non-limiting example, the lipid nanoparticle comprises the block copolymer PEG-PLGA-PEG (see e.g., the thermosensitive hydrogel (PEG-PLGA-PEG) was used as a TGF-beta1 gene delivery vehicle in Lee et al. Thermosensitive Hydrogel as a Tgf-β1 Gene Delivery Vehicle Enhances Diabetic Wound Healing. Pharmaceutical Research, 2003 20(12): 1995-2000; as a controlled gene delivery system in Li et al. Controlled Gene Delivery System Based on Thermosensitive Biodegradable Hydrogel. Pharmaceutical Research 2003 20(6):884-888; and Chang et al., Non-ionic amphiphilic biodegradable PEG-PLGA-PEG copolymer enhances gene delivery efficiency in rat skeletal muscle. J Controlled Release. 2007 118:245-253, the contents of each of which are herein incorporated by reference in their entirety). The RNA (e.g., mRNA) vaccines of the present disclosure may be formulated in lipid nanoparticles comprising the PEG-PLGA-PEG block copolymer.

In some embodiments, the therapeutic nanoparticle may comprise a multiblock copolymer (see e.g., U.S. Pat. Nos. 8,263,665 and 8,287,910 and U.S. Patent Pub. No. US20130195987, the contents of each of which are herein incorporated by reference in their entirety).

In some embodiments, the block copolymers described herein may be included in a polyion complex comprising a non-polymeric micelle and the block copolymer. (see e.g., U.S. Publication No. 20120076836, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the therapeutic nanoparticle may comprise at least one acrylic polymer. Acrylic polymers include but are not limited to, acrylic acid, methacrylic acid,

acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, amino alkyl methacrylate copolymer, poly (acrylic acid), poly(methacrylic acid), polycyanoacrylates and combinations thereof.

In some embodiments, the therapeutic nanoparticles may comprise at least one poly(vinyl ester) polymer. The poly (vinyl ester) polymer may be a copolymer such as a random copolymer. As a non-limiting example, the random copolymer may have a structure such as those described in International Application No. WO2013032829 or U.S. Patent Publication No US20130121954, the contents of each of which are herein incorporated by reference in their entirety. In some embodiments, the poly(vinyl ester) polymers may be conjugated to the polynucleotides described herein.

In some embodiments, the therapeutic nanoparticle may comprise at least one diblock copolymer. The diblock copolymer may be, but it not limited to, a poly(lactic) acid-poly (ethylene)glycol copolymer (see, e.g., International Patent Publication No. WO2013044219, the contents of which are herein incorporated by reference in their entirety).

As a non-limiting example, the therapeutic nanoparticle may be used to treat cancer (see International publication No. WO2013044219, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the therapeutic nanoparticles may comprise at least one cationic polymer described herein and/or known in the art.

In some embodiments, the therapeutic nanoparticles may comprise at least one amine-containing polymer such as, but not limited to polylysine, polyethylene imine, poly(amidoamine) dendrimers, poly(beta-amino esters) (see, e.g., U.S. Pat. No. 8,287,849, the contents of which are herein incorporated by reference in their entirety) and combinations thereof.

In some embodiments, the nanoparticles described herein may comprise an amine cationic lipid such as those described in International Patent Application No. WO2013059496, the contents of which are herein incorporated by reference in their entirety. In some embodiments, the cationic lipids may have an amino-amine or an amino-amide moiety.

In some embodiments, the therapeutic nanoparticles may comprise at least one degradable polyester which may contain polycationic side chains. Degradeable polyesters include, but are not limited to, poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester), and combinations thereof. In some embodiments, the degradable polyesters may include a PEG conjugation to form a PEGylated polymer.

In some embodiments, the synthetic nanocarriers may contain an immunostimulatory agent to enhance the immune response from delivery of the synthetic nanocarrier. As a non-limiting example, the synthetic nanocarrier may comprise a Th1 immunostimulatory agent, which may enhance a Th1-based response of the immune system (see International Pub No. WO2010123569 and U.S. Publication No. US20110223201, the contents of each of which are herein incorporated by reference in their entirety).

In some embodiments, the synthetic nanocarriers may be formulated for targeted release. In some embodiments, the synthetic nanocarrier is formulated to release the polynucleotides at a specified pH and/or after a desired time interval. As a non-limiting example, the synthetic nanoparticle may be formulated to release the RNA (e.g., mRNA) vaccines after 24 hours and/or at a pH of 4.5 (see International Publication Nos. WO2010138193 and WO2010138194 and US Pub Nos. US20110020388 and US20110027217, each of which is herein incorporated by reference in their entireties).

In some embodiments, the synthetic nanocarriers may be formulated for controlled and/or sustained release of the polynucleotides described herein. As a non-limiting example, the synthetic nanocarriers for sustained release may be formulated by methods known in the art, described herein and/or as described in International Pub No. WO2010138192 and US Pub No. 20100303850, each of which is herein incorporated by reference in their entirety.

In some embodiments, the RNA (e.g., mRNA) vaccine may be formulated for controlled and/or sustained release wherein the formulation comprises at least one polymer that is a crystalline side chain (CYSC) polymer. CYSC polymers are described in U.S. Pat. No. 8,399,007, herein incorporated by reference in its entirety.

In some embodiments, the synthetic nanocarrier may be formulated for use as a vaccine. In some embodiments, the synthetic nanocarrier may encapsulate at least one polynucleotide which encode at least one antigen. As a non-limiting example, the synthetic nanocarrier may include at least one antigen and an excipient for a vaccine dosage form (see International Publication No. WO2011150264 and U.S. Publication No. US20110293723, the contents of each of which are herein incorporated by reference in their entirety). As another non-limiting example, a vaccine dosage form may include at least two synthetic nanocarriers with the same or different antigens and an excipient (see International Publication No. WO2011150249 and U.S. Publication No. US20110293701, the contents of each of which are herein incorporated by reference in their entirety). The vaccine dosage form may be selected by methods described herein, known in the art and/or described in International Publication No. WO2011150258 and U.S. Publication No. US20120027806, the contents of each of which are herein incorporated by reference in their entirety).

In some embodiments, the synthetic nanocarrier may comprise at least one polynucleotide which encodes at least one adjuvant. As non-limiting example, the adjuvant may comprise dimethyldioctadecylammonium-bromide, dimethyldioctadecylammonium-chloride, dimethyldioctadecylammonium-phosphate or dimethyldioctadecylammonium-acetate (DDA) and an apolar fraction or part of said apolar fraction of a total lipid extract of a *mycobacterium* (see, e.g., U.S. Pat. No. 8,241,610, the content of which is herein incorporated by reference in its entirety). In some embodiments, the synthetic nanocarrier may comprise at least one polynucleotide and an adjuvant. As a non-limiting example, the synthetic nanocarrier comprising and adjuvant may be formulated by the methods described in International Publication No. WO2011150240 and U.S. Publication No. US20110293700, the contents of each of which are herein incorporated by reference in their entirety.

In some embodiments, the synthetic nanocarrier may encapsulate at least one polynucleotide that encodes a peptide, fragment or region from a virus. As a non-limiting example, the synthetic nanocarrier may include, but is not limited to, any of the nanocarriers described in International Publication No. WO2012024621, WO201202629, WO2012024632 and U.S. Publication No. US20120064110, US20120058153 and US20120058154, the contents of each of which are herein incorporated by reference in their entirety.

In some embodiments, the synthetic nanocarrier may be coupled to a polynucleotide which may be able to trigger a humoral and/or cytotoxic T lymphocyte (CTL) response

(see, e.g., International Publication No. WO2013019669, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the RNA (e.g., mRNA) vaccine may be encapsulated in, linked to and/or associated with zwitterionic lipids. Non-limiting examples of zwitterionic lipids and methods of using zwitterionic lipids are described in U.S. Patent Publication No. US20130216607, the contents of which are herein incorporated by reference in their entirety.

In some aspects, the zwitterionic lipids may be used in the liposomes and lipid nanoparticles described herein.

In some embodiments, the RNA (e.g., mRNA) vaccine may be formulated in colloid nanocarriers as described in U.S. Patent Publication No. US20130197100, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the nanoparticle may be optimized for oral administration. The nanoparticle may comprise at least one cationic biopolymer such as, but not limited to, chitosan or a derivative thereof. As a non-limiting example, the nanoparticle may be formulated by the methods described in U.S. Publication No. 20120282343, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, LNPs comprise the lipid KL52 (an amino-lipid disclosed in U.S. Application Publication No. 2012/0295832, the contents of which are herein incorporated by reference in their entirety. Activity and/or safety (as measured by examining one or more of ALT/AST, white blood cell count and cytokine induction, for example) of LNP administration may be improved by incorporation of such lipids. LNPs comprising KL52 may be administered intravenously and/or in one or more doses. In some embodiments, administration of LNPs comprising KL52 results in equal or improved mRNA and/or protein expression as compared to LNPs comprising MC3.

In some embodiments, RNA (e.g., mRNA) vaccine may be delivered using smaller LNPs. Such particles may comprise a diameter from below 0.1 um up to 100 nm such as, but not limited to, less than 0.1 um, less than 1.0 um, less than 5 um, less than 10 um, less than 15 um, less than 20 um, less than 25 um, less than 30 um, less than 35 um, less than 40 um, less than 50 um, less than 55 um, less than 60 um, less than 65 um, less than 70 um, less than 75 um, less than 80 um, less than 85 um, less than 90 um, less than 95 um, less than 100 um, less than 125 um, less than 150 um, less than 175 um, less than 200 um, less than 225 um, less than 250 um, less than 275 um, less than 300 um, less than 325 um, less than 350 um, less than 375 um, less than 400 um, less than 425 um, less than 450 um, less than 475 um, less than 500 um, less than 525 um, less than 550 um, less than 575 um, less than 600 um, less than 625 um, less than 650 um, less than 675 um, less than 700 um, less than 725 um, less than 750 um, less than 775 um, less than 800 um, less than 825 um, less than 850 um, less than 875 um, less than 900 um, less than 925 um, less than 950 um, less than 975 um, or less than 1000 um.

In some embodiments, RNA (e.g., mRNA) vaccines may be delivered using smaller LNPs, which may comprise a diameter from about 1 nm to about 100 nm, from about 1 nm to about 10 nm, about 1 nm to about 20 nm, from about 1 nm to about 30 nm, from about 1 nm to about 40 nm, from about 1 nm to about 50 nm, from about 1 nm to about 60 nm, from about 1 nm to about 70 nm, from about 1 nm to about 80 nm, from about 1 nm to about 90 nm, from about 5 nm to about from 100 nm, from about 5 nm to about 10 nm, about 5 nm to about 20 nm, from about 5 nm to about 30 nm, from about 5 nm to about 40 nm, from about 5 nm to about 50 nm, from about 5 nm to about 60 nm, from about 5 nm to about 70 nm, from about 5 nm to about 80 nm, from about 5 nm to about 90 nm, about 10 to about 50 nm, from about 20 to about 50 nm, from about 30 to about 50 nm, from about 40 to about 50 nm, from about 20 to about 60 nm, from about 30 to about 60 nm, from about 40 to about 60 nm, from about 20 to about 70 nm, from about 30 to about 70 nm, from about 40 to about 70 nm, from about 50 to about 70 nm, from about 60 to about 70 nm, from about 20 to about 80 nm, from about 30 to about 80 nm, from about 40 to about 80 nm, from about 50 to about 80 nm, from about 60 to about 80 nm, from about 20 to about 90 nm, from about 30 to about 90 nm, from about 40 to about 90 nm, from about 50 to about 90 nm, from about 60 to about 90 nm and/or from about 70 to about 90 nm.

In some embodiments, such LNPs are synthesized using methods comprising microfluidic mixers. Examples of microfluidic mixers may include, but are not limited to, a slit interdigital micromixer including, but not limited to those manufactured by Microinnova (Allerheiligen bei Wildon, Austria) and/or a staggered herringbone micromixer (SHM) (Zhigaltsev, I. V. et al., Bottom-up design and synthesis of limit size lipid nanoparticle systems with aqueous and triglyceride cores using millisecond microfluidic mixing have been published (Langmuir. 2012. 28:3633-40; Belliveau, N. M. et al., Microfluidic synthesis of highly potent limit-size lipid nanoparticles for in vivo delivery of siRNA. Molecular Therapy-Nucleic Acids. 2012. 1:e37; Chen, D. et al., Rapid discovery of potent siRNA-containing lipid nanoparticles enabled by controlled microfluidic formulation. J Am Chem Soc. 2012. 134(16):6948-51, the contents of each of which are herein incorporated by reference in their entirety). In some embodiments, methods of LNP generation comprising SHM, further comprise the mixing of at least two input streams wherein mixing occurs by microstructure-induced chaotic advection (MICA). According to this method, fluid streams flow through channels present in a herringbone pattern causing rotational flow and folding the fluids around each other. This method may also comprise a surface for fluid mixing wherein the surface changes orientations during fluid cycling. Methods of generating LNPs using SHM include those disclosed in U.S. Application Publication Nos. 2004/0262223 and 2012/0276209, the contents of each of which are herein incorporated by reference in their entirety.

In some embodiments, the RNA (e.g., mRNA) vaccine of the present disclosure may be formulated in lipid nanoparticles created using a micromixer such as, but not limited to, a Slit Interdigital Microstructured Mixer (SIMM-V2) or a Standard Slit Interdigital Micro Mixer (SSIMM) or Caterpillar (CPMM) or Impinging-jet (IJMM) from the Institut fiir Mikrotechnik Mainz GmbH, Mainz Germany).

In some embodiments, the RNA (e.g., mRNA) vaccines of the present disclosure may be formulated in lipid nanoparticles created using microfluidic technology (see, e.g., Whitesides, George M. The Origins and the Future of Microfluidics. Nature, 2006 442: 368-373; and Abraham et al. Chaotic Mixer for Microchannels. Science, 2002 295: 647-651; each of which is herein incorporated by reference in its entirety). As a non-limiting example, controlled microfluidic formulation includes a passive method for mixing streams of steady pressure-driven flows in micro channels at a low Reynolds number (see, e.g., Abraham et al. Chaotic Mixer for Microchannels. Science, 2002 295: 647-651, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the RNA (e.g., mRNA) vaccines of the present disclosure may be formulated in lipid nanoparticles created using a micromixer chip such as, but not limited to, those from Harvard Apparatus (Holliston, Mass.) or Dolomite Microfluidics (Royston, UK). A micromixer chip can be used for rapid mixing of two or more fluid streams with a split and recombine mechanism.

In some embodiments, the RNA (e.g., mRNA) vaccines of the disclosure may be formulated for delivery using the drug encapsulating microspheres described in International Patent Publication No. WO2013063468 or U.S. Pat. No. 8,440,614, the contents of each of which are herein incorporated by reference in their entirety. The microspheres may comprise a compound of the formula (I), (II), (III), (IV), (V) or (VI) as described in International Patent Publication No. WO2013063468, the contents of which are herein incorporated by reference in their entirety. In some embodiments, the amino acid, peptide, polypeptide, lipids (APPL) are useful in delivering the RNA (e.g., mRNA) vaccines of the disclosure to cells (see International Patent Publication No. WO2013063468, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the RNA (e.g., mRNA) vaccines of the disclosure may be formulated in lipid nanoparticles having a diameter from about 10 to about 100 nm such as, but not limited to, about 10 to about 20 nm, about 10 to about 30 nm, about 10 to about 40 nm, about 10 to about 50 nm, about 10 to about 60 nm, about 10 to about 70 nm, about 10 to about 80 nm, about 10 to about 90 nm, about 20 to about 30 nm, about 20 to about 40 nm, about 20 to about 50 nm, about 20 to about 60 nm, about 20 to about 70 nm, about 20 to about 80 nm, about 20 to about 90 nm, about 20 to about 100 nm, about 30 to about 40 nm, about 30 to about 50 nm, about 30 to about 60 nm, about 30 to about 70 nm, about 30 to about 80 nm, about 30 to about 90 nm, about 30 to about 100 nm, about 40 to about 50 nm, about 40 to about 60 nm, about 40 to about 70 nm, about 40 to about 80 nm, about 40 to about 90 nm, about 40 to about 100 nm, about 50 to about 60 nm, about 50 to about 70 nm about 50 to about 80 nm, about 50 to about 90 nm, about 50 to about 100 nm, about 60 to about 70 nm, about 60 to about 80 nm, about 60 to about 90 nm, about 60 to about 100 nm, about 70 to about 80 nm, about 70 to about 90 nm, about 70 to about 100 nm, about 80 to about 90 nm, about 80 to about 100 nm and/or about 90 to about 100 nm.

In some embodiments, the lipid nanoparticles may have a diameter from about 10 to 500 nm.

In some embodiments, the lipid nanoparticle may have a diameter greater than 100 nm, greater than 150 nm, greater than 200 nm, greater than 250 nm, greater than 300 nm, greater than 350 nm, greater than 400 nm, greater than 450 nm, greater than 500 nm, greater than 550 nm, greater than 600 nm, greater than 650 nm, greater than 700 nm, greater than 750 nm, greater than 800 nm, greater than 850 nm, greater than 900 nm, greater than 950 nm or greater than 1000 nm.

In some embodiments, the lipid nanoparticle may be a limit size lipid nanoparticle described in International Patent Publication No. WO2013059922, the contents of which are herein incorporated by reference in their entirety. The limit size lipid nanoparticle may comprise a lipid bilayer surrounding an aqueous core or a hydrophobic core; where the lipid bilayer may comprise a phospholipid such as, but not limited to, diacylphosphatidylcholine, a diacylphosphatidylethanolamine, a ceramide, a sphingomyelin, a dihydrosphingomyelin, a cephalin, a cerebroside, a C8-C20 fatty acid diacylphophatidylcholine, and 1-palmitoyl-2-oleoyl phosphatidylcholine (POPC). In some embodiments, the limit size lipid nanoparticle may comprise a polyethylene glycol-lipid such as, but not limited to, DLPE-PEG, DMPE-PEG, DPPC-PEG and DSPE-PEG.

In some embodiments, the RNA (e.g., mRNA) vaccines may be delivered, localized and/or concentrated in a specific location using the delivery methods described in International Patent Publication No. WO2013063530, the contents of which are herein incorporated by reference in their entirety. As a non-limiting example, a subject may be administered an empty polymeric particle prior to, simultaneously with or after delivering the RNA (e.g., mRNA) vaccines to the subject. The empty polymeric particle undergoes a change in volume once in contact with the subject and becomes lodged, embedded, immobilized or entrapped at a specific location in the subject.

In some embodiments, the RNA (e.g., mRNA) vaccines may be formulated in an active substance release system (see, e.g., U.S. Patent Publication No. US20130102545, the contents of which are herein incorporated by reference in their entirety). The active substance release system may comprise 1) at least one nanoparticle bonded to an oligonucleotide inhibitor strand which is hybridized with a catalytically active nucleic acid and 2) a compound bonded to at least one substrate molecule bonded to a therapeutically active substance (e.g., polynucleotides described herein), where the therapeutically active substance is released by the cleavage of the substrate molecule by the catalytically active nucleic acid.

In some embodiments, the RNA (e.g., mRNA) vaccines may be formulated in a nanoparticle comprising an inner core comprising a non-cellular material and an outer surface comprising a cellular membrane. The cellular membrane may be derived from a cell or a membrane derived from a virus. As a non-limiting example, the nanoparticle may be made by the methods described in International Patent Publication No. WO2013052167, the contents of which are herein incorporated by reference in their entirety. As another non-limiting example, the nanoparticle described in International Patent Publication No. WO2013052167, the contents of which are herein incorporated by reference in their entirety, may be used to deliver the RNA (e.g., mRNA) vaccines described herein.

In some embodiments, the RNA (e.g., mRNA) vaccines may be formulated in porous nanoparticle-supported lipid bilayers (protocells). Protocells are described in International Patent Publication No. WO2013056132, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the RNA (e.g., mRNA) vaccines described herein may be formulated in polymeric nanoparticles as described in or made by the methods described in U.S. Pat. Nos. 8,420,123 and 8,518,963 and European Patent No. EP2073848B1, the contents of each of which are herein incorporated by reference in their entirety. As a non-limiting example, the polymeric nanoparticle may have a high glass transition temperature such as the nanoparticles described in or nanoparticles made by the methods described in U.S. Pat. No. 8,518,963, the contents of which are herein incorporated by reference in their entirety. As another non-limiting example, the polymer nanoparticle for oral and parenteral formulations may be made by the methods described in European Patent No. EP2073848B1, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the RNA (e.g., mRNA) vaccines described herein may be formulated in nanoparticles used in imaging. The nanoparticles may be liposome nanoparticles

such as those described in U.S. Patent Publication No US20130129636, herein incorporated by reference in its entirety. As a non-limiting example, the liposome may comprise gadolinium(III)2-{4,7-bis-carboxymethyl-10-[(N, N-distearylamidomethyl-N'-amido-methyl]-1,4,7,10-tetra-azacyclododec-1-yl}-acetic acid and a neutral, fully saturated phospholipid component (see, e.g., U.S. Patent Publication No US20130129636, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the nanoparticles which may be used in the present disclosure are formed by the methods described in U.S. Patent Application No. US20130130348, the contents of which are herein incorporated by reference in their entirety.

The nanoparticles of the present disclosure may further include nutrients such as, but not limited to, those which deficiencies can lead to health hazards from anemia to neural tube defects (see, e.g., the nanoparticles described in International Patent Publication No WO2013072929, the contents of which are herein incorporated by reference in their entirety). As a non-limiting example, the nutrient may be iron in the form of ferrous, ferric salts or elemental iron, iodine, folic acid, vitamins or micronutrients.

In some embodiments, the RNA (e.g., mRNA) vaccines of the present disclosure may be formulated in a swellable nanoparticle. The swellable nanoparticle may be, but is not limited to, those described in U.S. Pat. No. 8,440,231, the contents of which are herein incorporated by reference in their entirety. As a non-limiting embodiment, the swellable nanoparticle may be used for delivery of the RNA (e.g., mRNA) vaccines of the present disclosure to the pulmonary system (see, e.g., U.S. Pat. No. 8,440,231, the contents of which are herein incorporated by reference in their entirety).

The RNA (e.g., mRNA) vaccines of the present disclosure may be formulated in polyanhydride nanoparticles such as, but not limited to, those described in U.S. Pat. No. 8,449,916, the contents of which are herein incorporated by reference in their entirety.

The nanoparticles and microparticles of the present disclosure may be geometrically engineered to modulate macrophage and/or the immune response. In some embodiments, the geometrically engineered particles may have varied shapes, sizes and/or surface charges in order to incorporated the polynucleotides of the present disclosure for targeted delivery such as, but not limited to, pulmonary delivery (see, e.g., International Publication No WO2013082111, the contents of which are herein incorporated by reference in their entirety). Other physical features the geometrically engineering particles may have include, but are not limited to, fenestrations, angled arms, asymmetry and surface roughness, charge which can alter the interactions with cells and tissues. As a non-limiting example, nanoparticles of the present disclosure may be made by the methods described in International Publication No WO2013082111, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the nanoparticles of the present disclosure may be water soluble nanoparticles such as, but not limited to, those described in International Publication No. WO2013090601, the contents of which are herein incorporated by reference in their entirety. The nanoparticles may be inorganic nanoparticles which have a compact and zwitterionic ligand in order to exhibit good water solubility. The nanoparticles may also have small hydrodynamic diameters (HD), stability with respect to time, pH, and salinity and a low level of non-specific protein binding.

In some embodiments the nanoparticles of the present disclosure may be developed by the methods described in U.S. Patent Publication No. US20130172406, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the nanoparticles of the present disclosure are stealth nanoparticles or target-specific stealth nanoparticles such as, but not limited to, those described in U.S. Patent Publication No. US20130172406, the contents of which are herein incorporated by reference in their entirety. The nanoparticles of the present disclosure may be made by the methods described in U.S. Patent Publication No. US20130172406, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the stealth or target-specific stealth nanoparticles may comprise a polymeric matrix. The polymeric matrix may comprise two or more polymers such as, but not limited to, polyethylenes, polycarbonates, polyanhydrides, polyhydroxyacids, polypropylfumerates, polycaprolactones, polyamides, polyacetals, polyethers, polyesters, poly(orthoesters), polycyanoacrylates, polyvinyl alcohols, polyurethanes, polyphosphazenes, polyacrylates, polymethacrylates, polycyanoacrylates, polyureas, polystyrenes, polyamines, polyesters, polyanhydrides, polyethers, polyurethanes, polymethacrylates, polyacrylates, polycyanoacrylates or combinations thereof.

In some embodiments, the nanoparticle may be a nanoparticle-nucleic acid hybrid structure having a high density nucleic acid layer. As a non-limiting example, the nanoparticle-nucleic acid hybrid structure may made by the methods described in U.S. Patent Publication No. US20130171646, the contents of which are herein incorporated by reference in their entirety. The nanoparticle may comprise a nucleic acid such as, but not limited to, polynucleotides described herein and/or known in the art.

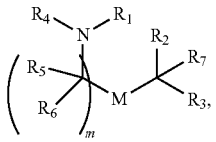
At least one of the nanoparticles of the present disclosure may be embedded in in the core a nanostructure or coated with a low density porous 3-D structure or coating which is capable of carrying or associating with at least one payload within or on the surface of the nanostructure. Non-limiting examples of the nanostructures comprising at least one nanoparticle are described in International Patent Publication No. WO2013123523, the contents of which are herein incorporated by reference in their entirety.

In some embodiments the RNA (e.g., mRNA) vaccine may be associated with a cationic or polycationic compounds, including protamine, nucleoline, spermine or spermidine, or other cationic peptides or proteins, such as poly-L-lysine (PLL), polyarginine, basic polypeptides, cell penetrating peptides (CPPs), including HIV-binding peptides, HIV-1 Tat (HIV), Tat-derived peptides, Penetratin, VP^{22} derived or analog peptides, Pestivirus Erns, HSV, VP^{22} (Herpes simplex), MAP, KALA or protein transduction domains (PTDs), PpT620, prolin-rich peptides, arginine-rich peptides, lysine-rich peptides, MPG-peptide(s), Pep-1, L-oligomers, Calcitonin peptide(s), Antennapedia-derived peptides (particularly from *Drosophila antennapedia*), pAntp, pIsl, FGF, Lactoferrin, Transportan, Buforin-2, Bac715-24, SynB, SynB(1), pVEC, hCT-derived peptides, SAP, histones, cationic polysaccharides, for example chitosan, polybrene, cationic polymers, e.g. polyethyleneimine (PEI), cationic lipids, e.g. DOTMA: [1-(2,3-sioleyloxy) propyl)]-N,N,N-trimethylammonium chloride, DMRIE, di-C14-amidine, DOTIM, SAINT, DC-Chol, BGTC, CTAP, DOPC, DODAP, DOPE: Dioleyl phosphatidylethanolamine, DOSPA, DODAB, DOIC, DMEPC, DOGS: Dioctadecylamidoglicylspermin, DIMRI: Dimyristooxypropyl

dimethyl hydroxyethyl ammonium bromide, DOTAP: dioleoyloxy-3-(trimethylammonio)propane, DC-6-14: O,O-ditetradecanoyl-N-.alpha.-trimethylammonioacetyl)diethanolamine chloride, CLIP 1: rac-[(2,3-dioctadecyloxypropyl)(2-hydroxyethyl)]-dimethylammonium chloride, CLIP6: rac-[2(2,3-dihexadecyloxypropyloxymethyloxy)ethyl]-trimethylammonium, CLIP9: rac-[2(2,3-dihexadecyloxypropyloxysuccinyloxy)ethyl]-trimethylammonium, oligofectamine, or cationic or polycationic polymers, e.g. modified polyaminoacids, such as beta-aminoacid-polymers or reversed polyamides, etc., modified polyethylenes, such as PVP (poly(N-ethyl-4-vinylpyridinium bromide)), etc., modified acrylates, such as pDMAEMA (poly(dimethylaminoethyl methylacrylate)), etc., modified amidoamines such as pAMAM (poly(amidoamine)), etc., modified polybetaminoester (PBAE), such as diamine end modified 1,4 butanediol diacrylate-co-5-amino-1-pentanol polymers, etc., dendrimers, such as polypropylamine dendrimers or pAMAM based dendrimers, etc., polyimine(s), such as PEI: poly(ethyleneimine), poly(propyleneimine), etc., polyallylamine, sugar backbone based polymers, such as cyclodextrin based polymers, dextran based polymers, chitosan, etc., silan backbone based polymers, such as PMOXA-PDMS copolymers, etc., blockpolymers consisting of a combination of one or more cationic blocks (e.g. selected from a cationic polymer as mentioned above) and of one or more hydrophilic or hydrophobic blocks (e.g. polyethyleneglycole), etc.

In other embodiments the RNA (e.g., mRNA) vaccine is not associated with a cationic or polycationic compounds.

In some embodiments, a nanoparticle comprises compounds of Formula (I):



(I)

or a salt or isomer thereof, wherein:

R_1 is selected from the group consisting of C_{5-30} alkyl, C_{5-20} alkenyl, —R*YR", —YR", and —R"M'R';

R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, C_{2-14} alkenyl, —R*YR", —YR", and —R*OR", or R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle;

R_4 is selected from the group consisting of a C_{3-6} carbocycle, $—(CH_2)_nQ$, $—(CH_2)_nCHQR$, —CHQR, $—CQ(R)_2$, and unsubstituted C_{1-6} alkyl, where Q is selected from a carbocycle, heterocycle, —OR, $—O(CH_2)_nN(R)_2$, —C(O)OR, —OC(O)R, $—CX_3$, $—CX_2H$, $—CXH_2$, —CN, $—N(R)_2$, $—C(O)N(R)_2$, $—N(R)C(O)R$, $—N(R)S(O)_2R$, $—N(R)C(O)N(R)_2$, $—N(R)C(S)N(R)_2$, $—N(R)R_8$, $—O(CH_2)_nOR$, $—N(R)C(=NR_9)N(R)_2$, $—N(R)C(=CHR_9)N(R)_2$, $—OC(O)N(R)_2$, $—N(R)C(O)OR$, $—N(OR)C(O)R$, $—N(OR)S(O)_2R$, $—N(OR)C(O)OR$, $—N(OR)C(O)N(R)_2$, $—N(OR)C(S)N(R)_2$, $—N(OR)C(=NR_9)N(R)_2$, $—N(OR)C(=CHR_9)N(R)_2$, $—C(=NR_9)N(R)_2$, $—C(=NR_9)R$, —C(O)N(R)O R, and $—C(R)N(R)_2C(O)OR$, and each n is independently selected from 1, 2, 3, 4, and 5;

each R_5 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R_6 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

M and M' are independently selected from —C(O)O—, —OC(O)—, —C(O)N(R')—, —N(R')C(O)—, —C(O)—, —C(S)—, —C(S)S—, —SC(S)—, —CH(OH)—, —P(O)(OR')O—, $—S(O)_2—$, —S—S—, an aryl group, and a heteroaryl group;

R_7 is selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H; R_8 is selected from the group consisting of C_{3-6} carbocycle and heterocycle;

R_9 is selected from the group consisting of H, CN, NO_2, C_{1-6} alkyl, —OR, $—S(O)_2R$, $—S(O)_2N(R)_2$, C_{2-6} alkenyl, C_{3-6} carbocycle and heterocycle;

each R is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R' is independently selected from the group consisting of C_{1-18} alkyl, C_{2-18} alkenyl, —R*YR", —YR", and H;

each R" is independently selected from the group consisting of C_{3-14} alkyl and C_{3-14} alkenyl;

each R* is independently selected from the group consisting of C_{1-12} alkyl and C_{2-12} alkenyl;

each Y is independently a C_{3-6} carbocycle;

each X is independently selected from the group consisting of F, Cl, Br, and I; and

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13.

In some embodiments, a subset of compounds of Formula (I) includes those in which when R_4 is $—(CH_2)_nQ$, $—(CH_2)_nCHQR$, —CHQR, or $—CQ(R)_2$, then (i) Q is not $—N(R)_2$ when n is 1, 2, 3, 4 or 5, or (ii) Q is not 5, 6, or 7-membered heterocycloalkyl when n is 1 or 2.

In some embodiments, another subset of compounds of Formula (I) includes those in which

R_1 is selected from the group consisting of C_{5-30} alkyl, C_{5-20} alkenyl, —R*YR", —YR", and —R"M'R';

R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, C_{2-14} alkenyl, —R*YR", —YR", and —R*OR", or R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle;

R_4 is selected from the group consisting of a C_{3-6} carbocycle, $—(CH_2)_nQ$, $—(CH_2)_nCHQR$, —CHQR, $—CQ(R)_2$, and unsubstituted C_{1-6} alkyl, where Q is selected from a C_{3-6} carbocycle, a 5- to 14-membered heteroaryl having one or more heteroatoms selected from N, O, and S, —OR, $—O(CH_2)N(R)_2$, —C(O)OR, —OC(O)R, $—CX_3$, $—CX_2H$, $—CXH_2$, —CN, $—C(O)N(R)_2$, $—N(R)C(O)R$, $—N(R)S(O)_2R$, $—N(R)C(O)N(R)_2$, $—N(R)C(S)N(R)_2$, $—CRN(R)_2C(O)OR$, $—N(R)R_8$, $—O(CH_2)_nOR$, $—N(R)C(=NR_9)N(R)_2$, $—N(R)C(=CHR_9)N(R)_2$, $—OC(O)N(R)_2$, $—N(R)C(O)OR$, $—N(OR)C(O)R$, $—N(OR)S(O)_2R$, $—N(OR)C(O)OR$, $—N(OR)C(O)N(R)_2$, $—N(OR)C(S)N(R)_2$, $—N(OR)C(=NR_9)N(R)_2$, $—N(OR)C(=CHR_9)N(R)_2$, $—C(=NR_9)N(R)_2$, $—C(=NR_9)R$, —C(O)N(R)O R, and a 5- to 14-membered heterocycloalkyl having one or more heteroatoms selected from N, O, and S which is substituted with one or more substituents selected from oxo (=O), OH, amino, mono- or di-alkylamino, and C_{1-3} alkyl, and each n is independently selected from 1, 2, 3, 4, and 5;

each R_5 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R_6 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

M and M' are independently selected from —C(O)O—, —OC(O)—, —C(O)N(R')—, —N(R')C(O)—, —C(O)—, —C(S)—, —C(S)S—, —SC(S)—, —CH(OH)—, —P(O)(OR')O—, $—S(O)_2—$, —S—S—, an aryl group, and a heteroaryl group;

R_7 is selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

R_8 is selected from the group consisting of C_{3-6} carbocycle and heterocycle;

R_9 is selected from the group consisting of H, CN, NO_2, C_{1-6} alkyl, —OR, —$S(O)_2R$, —$S(O)_2N(R)_2$, C_{2-6} alkenyl, C_{3-6} carbocycle and heterocycle;

each R is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R' is independently selected from the group consisting of C_{1-18} alkyl, C_{2-18} alkenyl, —R*YR", —YR", and H;

each R" is independently selected from the group consisting of C_{3-14} alkyl and C_{3-14} alkenyl;

each R* is independently selected from the group consisting of C_{1-12} alkyl and C_{2-12} alkenyl;

each Y is independently a C_{3-6} carbocycle;

each X is independently selected from the group consisting of F, Cl, Br, and I; and

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13,

or salts or isomers thereof.

In some embodiments, another subset of compounds of Formula (I) includes those in which

R_1 is selected from the group consisting of C_{5-30} alkyl, C_{5-20} alkenyl, —R*YR", —YR", and —R"M'R';

R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, C_{2-14} alkenyl, —R*YR", —YR", and —R*OR", or R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle;

R_4 is selected from the group consisting of a C_{3-6} carbocycle, —$(CH_2)_nQ$, —$(CH_2)_nCHQR$, —CHQR, —$CQ(R)_2$, and unsubstituted C_{1-6} alkyl, where Q is selected from a C_{3-6} carbocycle, a 5- to 14-membered heterocycle having one or more heteroatoms selected from N, O, and S, —OR, —$O(CH_2)_nN(R)_2$, —C(O)OR, —OC(O)R, —CX_3, —CX_2H, —CXH_2, —CN, —$C(O)N(R)_2$, —N(R)C(O)R, —$N(R)S(O)_2R$, —N(R)C(O)$N(R)_2$, —N(R)C(S)$N(R)_2$, —$CRN(R)_2C(O)OR$, —$N(R)R_8$, —$O(CH_2)_nOR$, —N(R)C(=NR_9)$N(R)_2$, —N(R)C(=CHR_9)$N(R)_2$, —$OC(O)N(R)_2$, —N(R)C(O)OR, —N(OR)C(O)R, —$N(OR)S(O)_2R$, —N(OR)C(O)OR, —N(OR)C(O)$N(R)_2$, —N(OR)C(S)$N(R)_2$, —N(OR)C(=NR_9)$N(R)_2$, —N(OR)C(=CHR_9)$N(R)_2$, —C(=NR_9)R, —C(O)N(R)OR, and —C(=NR_9)$N(R)_2$, and each n is independently selected from 1, 2, 3, 4, and 5; and when Q is a 5- to 14-membered heterocycle and (i) R_4 is —$(CH_2)_nQ$ in which n is 1 or 2, or (ii) R_4 is —$(CH_2)_nCHQR$ in which n is 1, or (iii) R_4 is —CHQR, and —$CQ(R)_2$, then Q is either a 5- to 14-membered heteroaryl or 8- to 14-membered heterocycloalkyl;

each R_5 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R_6 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

M and M' are independently selected from —C(O)O—, —OC(O)—, —C(O)N(R')—, —N(R')C(O)—, —C(O)—, —C(S)—, —C(S)S—, —SC(S)—, —CH(OH)—, —P(O)(OR')O—, —$S(O)_2$—, —S—S—, an aryl group, and a heteroaryl group;

R_7 is selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

R_8 is selected from the group consisting of C_{3-6} carbocycle and heterocycle;

R_9 is selected from the group consisting of H, CN, NO_2, C_{1-6} alkyl, —OR, —$S(O)_2R$, —$S(O)_2N(R)_2$, C_{2-6} alkenyl, C_{3-6} carbocycle and heterocycle;

each R is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R' is independently selected from the group consisting of C_{1-18} alkyl, C_{2-18} alkenyl, —R*YR", —YR", and H;

each R" is independently selected from the group consisting of C_{3-14} alkyl and C_{3-14} alkenyl;

each R* is independently selected from the group consisting of C_{1-12} alkyl and C_{2-12} alkenyl;

each Y is independently a C_{3-6} carbocycle;

each X is independently selected from the group consisting of F, Cl, Br, and I; and

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13,

or salts or isomers thereof.

In some embodiments, another subset of compounds of Formula (I) includes those in which

R_1 is selected from the group consisting of C_{5-30} alkyl, C_{5-20} alkenyl, —R*YR", —YR", and —R"M'R';

R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, C_{2-14} alkenyl, —R*YR", —YR", and —R*OR", or R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle;

R_4 is selected from the group consisting of a C_{3-6} carbocycle, —$(CH_2)_nQ$, —$(CH_2)_nCHQR$, —CHQR, —$CQ(R)_2$, and unsubstituted C_{1-6} alkyl, where Q is selected from a C_{3-6} carbocycle, a 5- to 14-membered heteroaryl having one or more heteroatoms selected from N, O, and S, —OR, —$O(CH_2)_nN(R)_2$, —C(O)OR, —OC(O)R, —CX_3, —CX_2H, —CXH_2, —CN, —$C(O)N(R)_2$, —N(R)C(O)R, —$N(R)S(O)_2R$, —N(R)C(O)$N(R)_2$, —N(R)C(S)$N(R)_2$, —$CRN(R)_2C(O)OR$, —$N(R)R_8$, —$O(CH_2)_nOR$, —N(R)C(=NR_9)$N(R)_2$, —N(R)C(=CHR_9)$N(R)_2$, —$OC(O)N(R)_2$, —N(R)C(O)OR, —N(OR)C(O)R, —$N(OR)S(O)_2R$, —N(OR)C(O)OR, —N(OR)C(O)$N(R)_2$, —N(OR)C(S)$N(R)_2$, —N(OR)C(=NR_9)$N(R)_2$, —N(OR)C(=CHR_9)$N(R)_2$, —C(=NR_9)R, —C(O)N(R)OR, and —C(=NR_9)$N(R)_2$, and each n is independently selected from 1, 2, 3, 4, and 5;

each R_5 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R_6 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

M and M' are independently selected from —C(O)O—, —OC(O)—, —C(O)N(R')—, —N(R')C(O)—, —C(O)—, —C(S)—, —C(S)S—, —SC(S)—, —CH(OH)—, —P(O)(OR')O—, —$S(O)_2$—, —S—S—, an aryl group, and a heteroaryl group;

R_7 is selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

R_8 is selected from the group consisting of C_{3-6} carbocycle and heterocycle;

R_9 is selected from the group consisting of H, CN, NO_2, C_{1-6} alkyl, —OR, —$S(O)_2R$, —$S(O)_2N(R)_2$, C_{2-6} alkenyl, C_{3-6} carbocycle and heterocycle;

each R is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R' is independently selected from the group consisting of C_{1-18} alkyl, C_{2-18} alkenyl, —R*YR", —YR", and H;

each R" is independently selected from the group consisting of C_{3-14} alkyl and C_{3-14} alkenyl;

each R* is independently selected from the group consisting of C_{1-12} alkyl and C_{2-12} alkenyl;

each Y is independently a C_{3-6} carbocycle;

each X is independently selected from the group consisting of F, Cl, Br, and I; and

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13,

or salts or isomers thereof.

In some embodiments, another subset of compounds of Formula (I) includes those in which

R_1 is selected from the group consisting of C_{5-30} alkyl, C_{5-20} alkenyl, —R*YR", —YR", and —R"M'R';

R_2 and R_3 are independently selected from the group consisting of H, C_{2-14} alkyl, C_{2-14} alkenyl, —R*YR", —YR", and —R*OR", or R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle;

R_4 is $—(CH_2)_nQ$ or $—(CH_2)_nCHQR$, where Q is $—N(R)_2$, and n is selected from 3, 4, and 5;

each R_5 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R_6 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

M and M' are independently selected from —C(O)O—, —OC(O)—, —C(O)N(R')—, —N(R')C(O)—, —C(O)—, —C(S)—, —C(S)S—, —SC(S)—, —CH(OH)—, —P(O)(OR')O—, $—S(O)_2—$, —S—S—, an aryl group, and a heteroaryl group;

R_7 is selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R' is independently selected from the group consisting of C_{1-18} alkyl, C_{2-18} alkenyl, —R*YR", —YR", and H;

each R" is independently selected from the group consisting of C_{3-14} alkyl and C_{3-14} alkenyl;

each R* is independently selected from the group consisting of C_{1-12} alkyl and C_{1-12} alkenyl;

each Y is independently a C_{3-6} carbocycle;

each X is independently selected from the group consisting of F, Cl, Br, and I; and

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13,

or salts or isomers thereof.

In some embodiments, another subset of compounds of Formula (I) includes those in which

R_1 is selected from the group consisting of C_{5-30} alkyl, C_{5-20} alkenyl, —R*YR", —YR", and —R"M'R';

R_2 and R_3 are independently selected from the group consisting of C_{1-14} alkyl, C_{2-14} alkenyl, —R*YR", —YR", and —R*OR", or R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle;

R_4 is selected from the group consisting of $—(CH_2)_nQ$, $—(CH_2)_nCHQR$, —CHQR, and $—CQ(R)_2$, where Q is $—N(R)_2$, and n is selected from 1, 2, 3, 4, and 5;

each R_5 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R_6 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

M and M' are independently selected from —C(O)O—, —OC(O)—, —C(O)N(R')—, —N(R')C(O)—, —C(O)—, —C(S)—, —C(S)S—, —SC(S)—, —CH(OH)—, —P(O)(OR')O—, $—S(O)_2—$, —S—S—, an aryl group, and a heteroaryl group;

R_7 is selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R' is independently selected from the group consisting of C_{1-18} alkyl, C_{2-18} alkenyl, —R*YR", —YR", and H;

each R" is independently selected from the group consisting of C_{3-14} alkyl and C_{3-14} alkenyl;

each R* is independently selected from the group consisting of C_{1-12} alkyl and C_{1-12} alkenyl;

each Y is independently a C_{3-6} carbocycle;

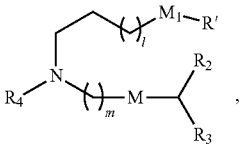
each X is independently selected from the group consisting of F, Cl, Br, and I; and

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13,

or salts or isomers thereof.

In some embodiments, a subset of compounds of Formula (I) includes those of Formula (IA):

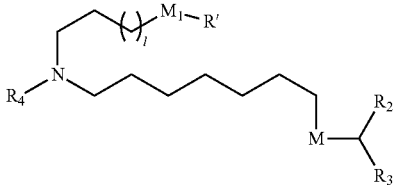
(IA)



or a salt or isomer thereof, wherein l is selected from 1, 2, 3, 4, and 5; m is selected from 5, 6, 7, 8, and 9; M_1 is a bond or M'; R_4 is unsubstituted C_{1-3} alkyl, or $—(CH_2)_nQ$, in which Q is OH, $—NHC(S)N(R)_2$, $—NHC(O)N(R)_2$, $—N(R)C(O)R$, $—N(R)S(O)_2R$, $—N(R)R_8$, $—NHC(=NR_9)N(R)_2$, $—NHC(=CHR_9)N(R)_2$, $—OC(O)N(R)_2$, $—N(R)C(O)OR$, heteroaryl or heterocycloalkyl; M and M' are independently selected from —C(O)O—, —OC(O)—, —C(O)N(R')—, —P(O)(OR')O—, —S—S—, an aryl group, and a heteroaryl group; and R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, and C_{2-14} alkenyl.

In some embodiments, a subset of compounds of Formula (I) includes those of Formula (II):

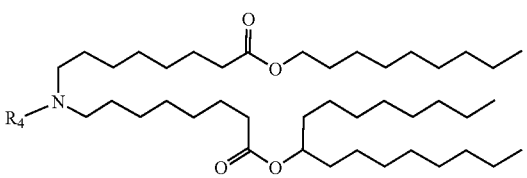
(II)



or a salt or isomer thereof, wherein l is selected from 1, 2, 3, 4, and 5; M_1 is a bond or M'; R_4 is unsubstituted C_{1-3} alkyl, or $—(CH_2)_nQ$, in which n is 2, 3, or 4, and Q is OH, $—NHC(S)N(R)_2$, $—NHC(O)N(R)_2$, $—N(R)C(O)R$, $—N(R)S(O)_2R$, $—N(R)R_8$, $—NHC(=NR_9)N(R)_2$, $—NHC(=CHR_9)N(R)_2$, $—OC(O)N(R)_2$, $—N(R)C(O)OR$, heteroaryl or heterocycloalkyl; M and M' are independently selected from —C(O)O—, —OC(O)—, —C(O)N(R')—, —P(O)(OR')O—, —S—S—, an aryl group, and a heteroaryl group; and R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, and C_{2-14} alkenyl.

In some embodiments, a subset of compounds of Formula (I) includes those of Formula (IIa), (IIb), (IIc), or (IIe):

(IIa)



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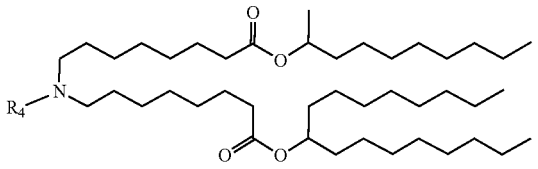
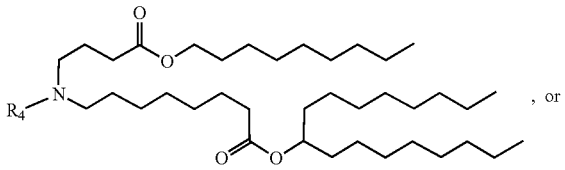
(IIb)

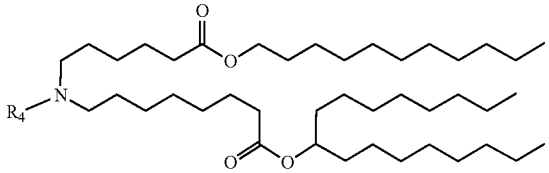


(IIc)



, or

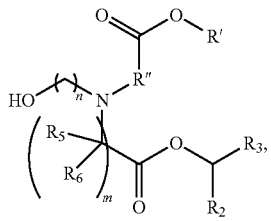
(IId)



or a salt or isomer thereof, wherein R_4 is as described herein.

In some embodiments, a subset of compounds of Formula (I) includes those of Formula (IId):

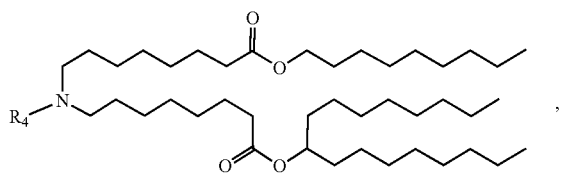
(IId)



or a salt or isomer thereof, wherein n is 2, 3, or 4; and m, R', R", and R_2 through R_6 are as described herein. For example, each of R_2 and R_3 may be independently selected from the group consisting of C_{5-14} alkyl and C_{5-14} alkenyl.

In some embodiments, a subset of compounds of Formula (I) includes those of Formula (IIa), (IIb), (IIc), or (IIe):

(IIa)



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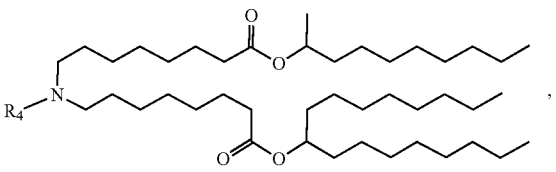
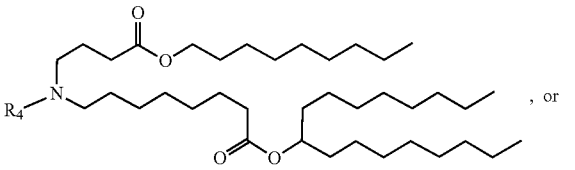
(IIb)

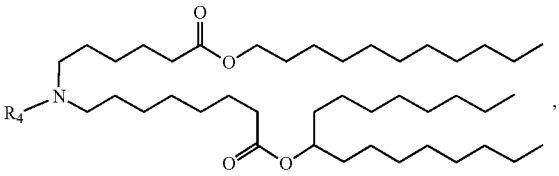


(IIc)



, or

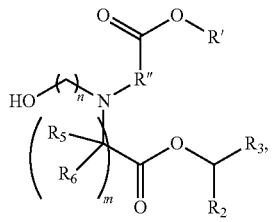
(IId)



or a salt or isomer thereof, wherein R_4 is as described herein.

In some embodiments, a subset of compounds of Formula (I) includes those of Formula (IId):

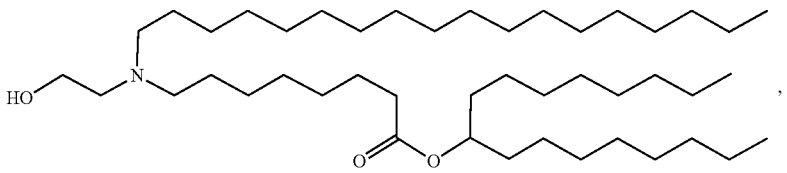
(IId)



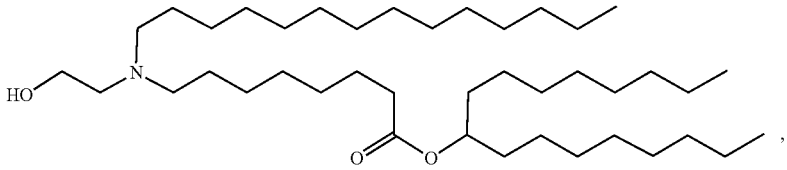
or a salt or isomer thereof, wherein n is 2, 3, or 4; and m, R', R", and R_2 through R_6 are as described herein. For example, each of R_2 and R_3 may be independently selected from the group consisting of C_{5-14} alkyl and C_{5-14} alkenyl.

In some embodiments, the compound of Formula (I) is selected from the group consisting of:

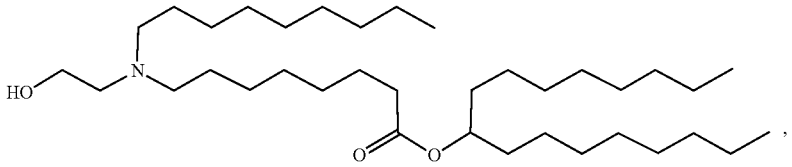
(Compound 1)



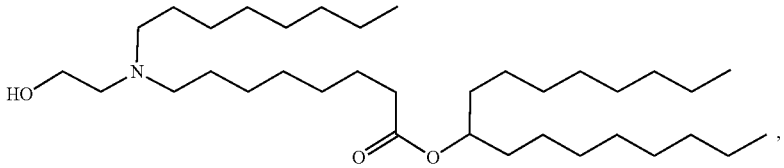
(Compound 2)



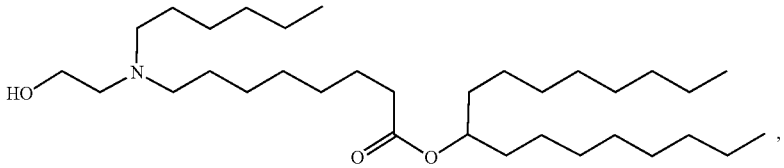
(Compound 3)



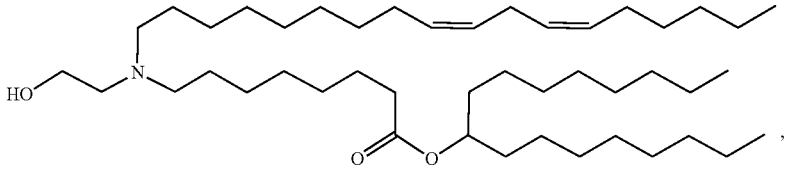
(Compound 4)



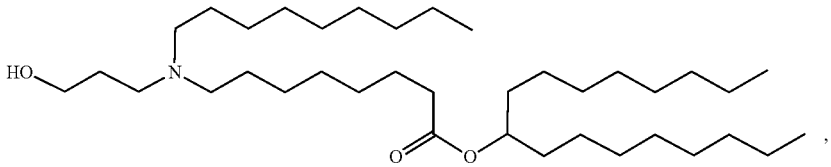
(Compound 5)



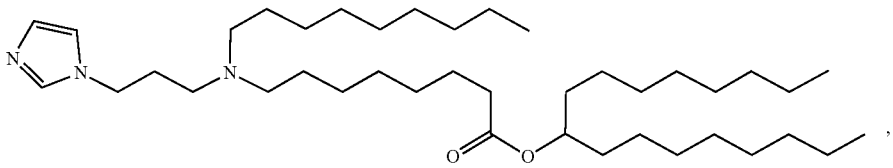
(Compound 6)



(Compound 7)



(Compound 8)



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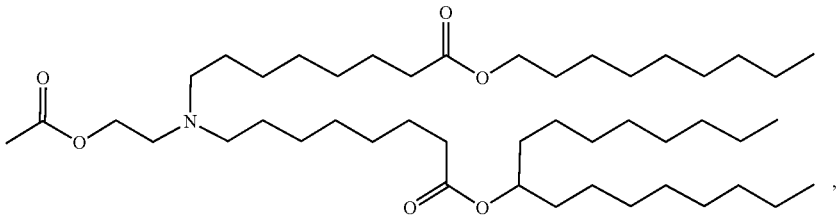

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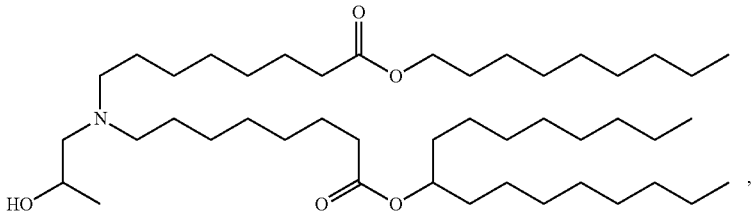

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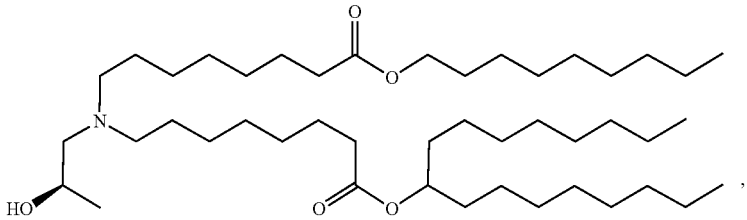

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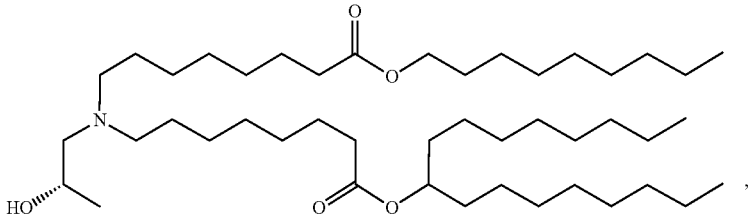

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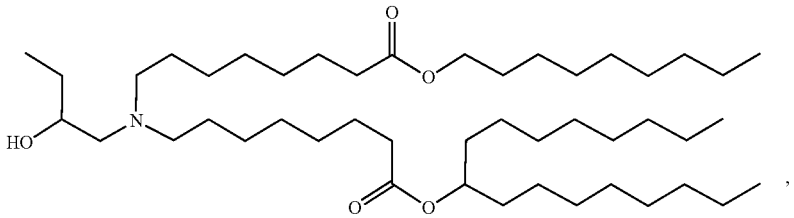

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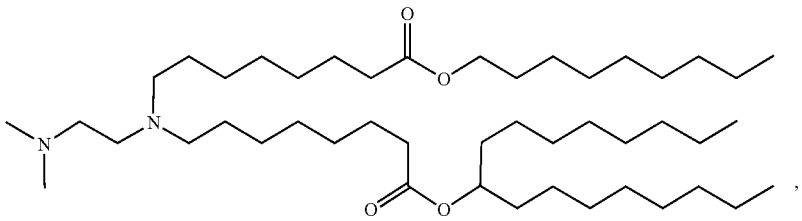

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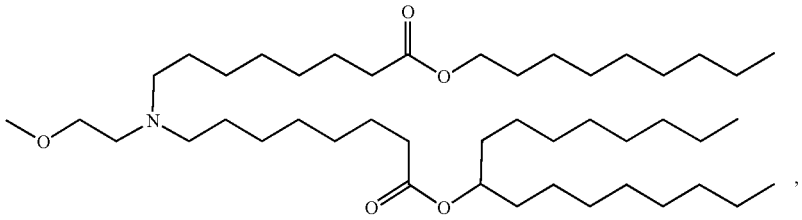

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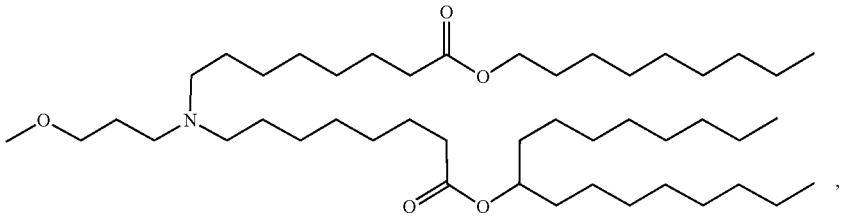

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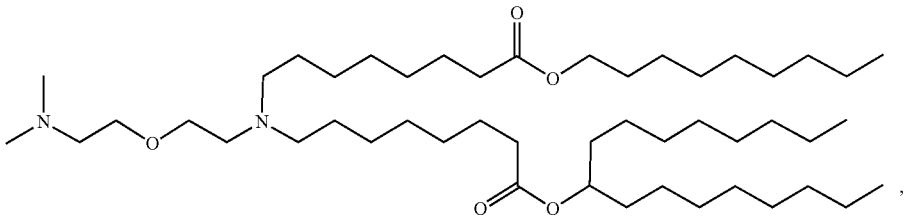

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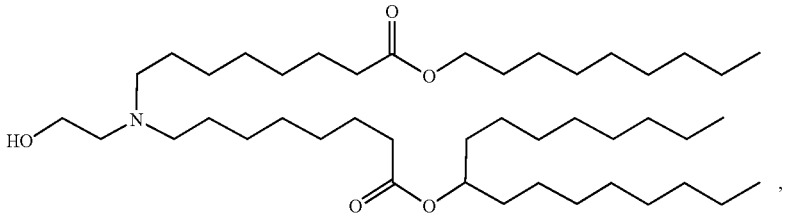

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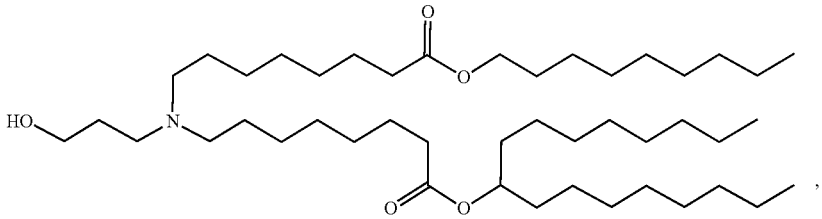

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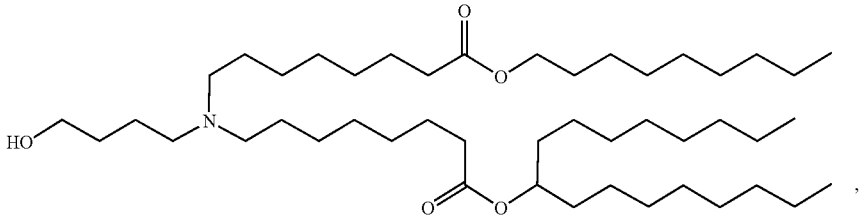

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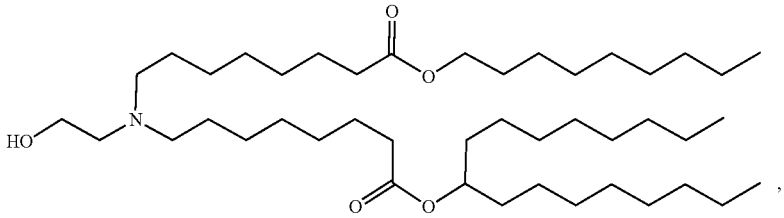

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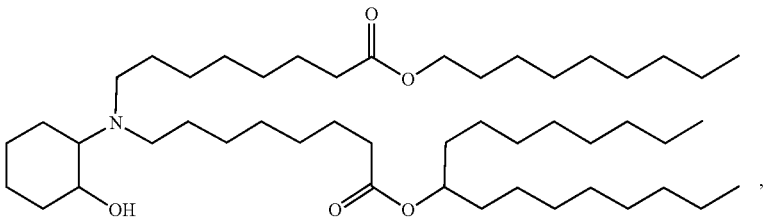

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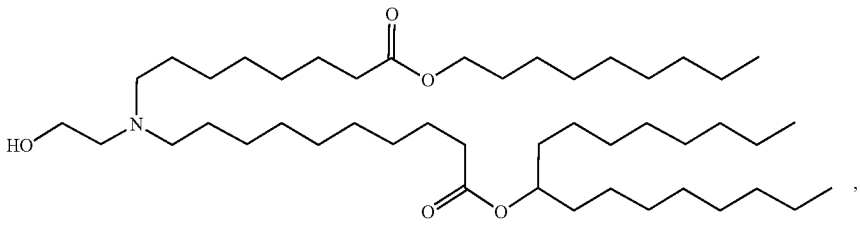

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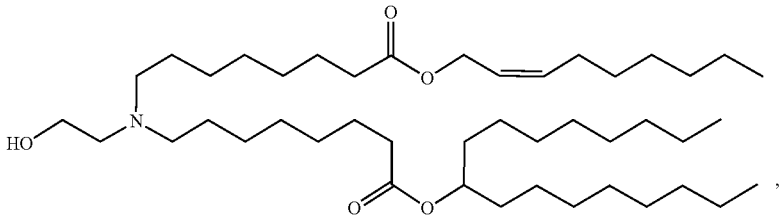

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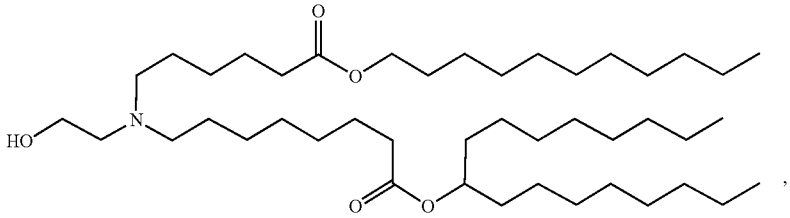

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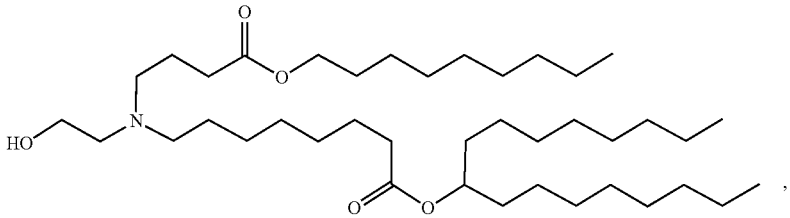

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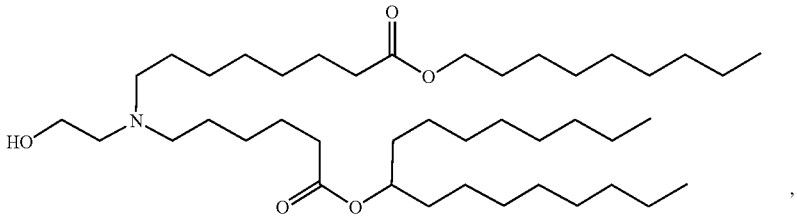

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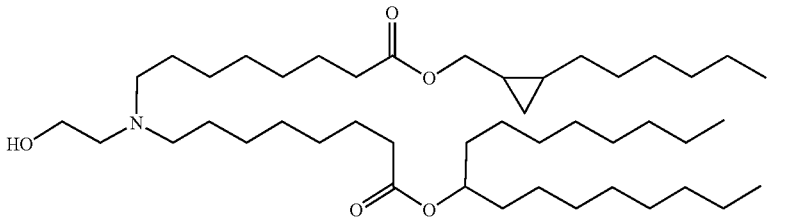

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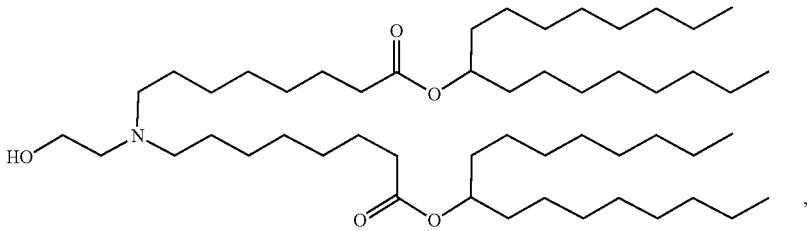

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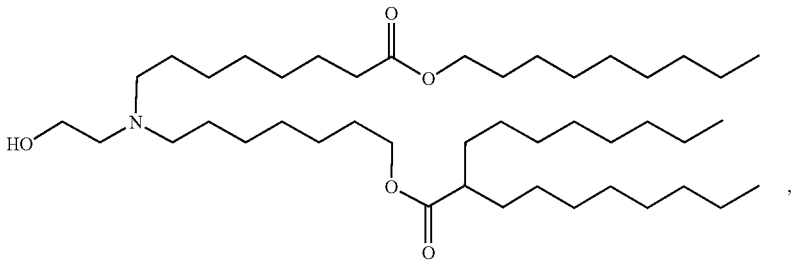

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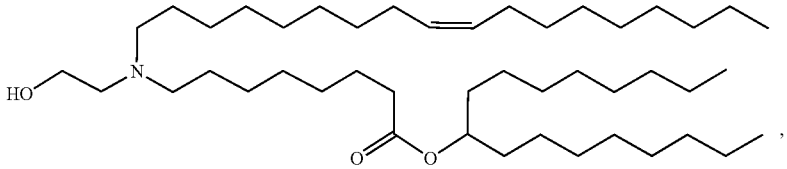

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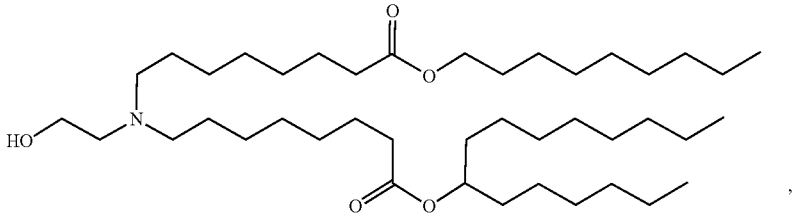

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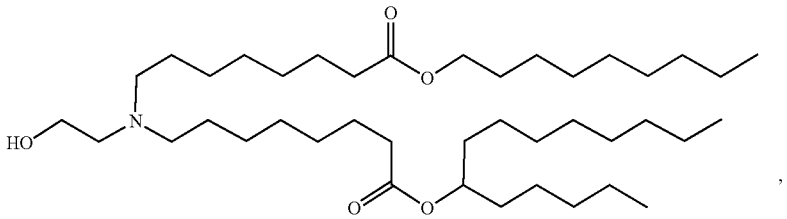

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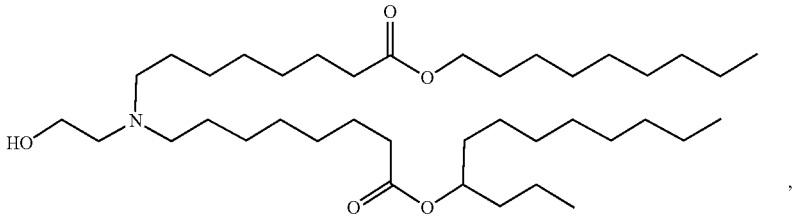

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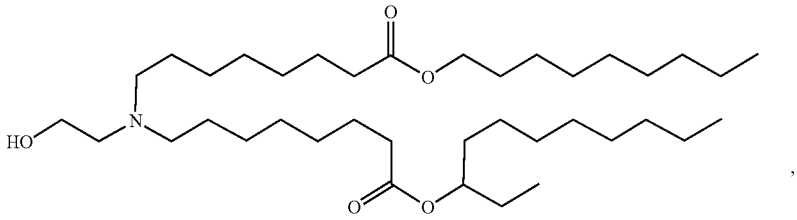

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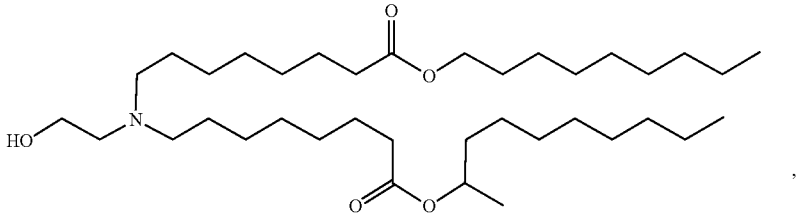

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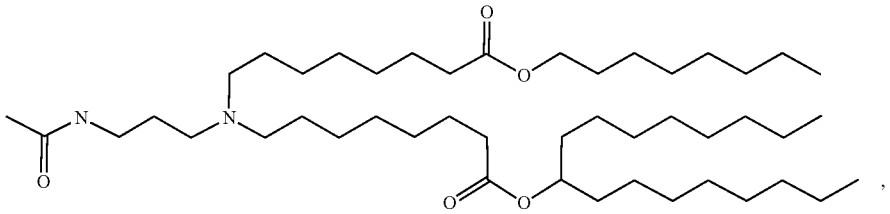

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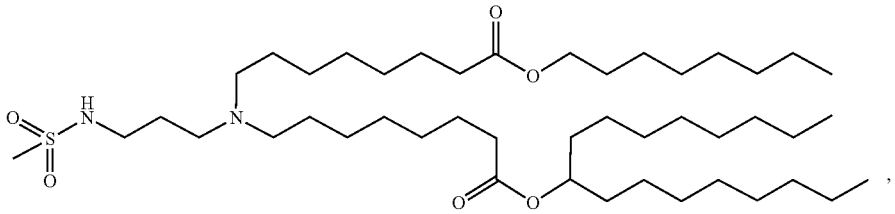

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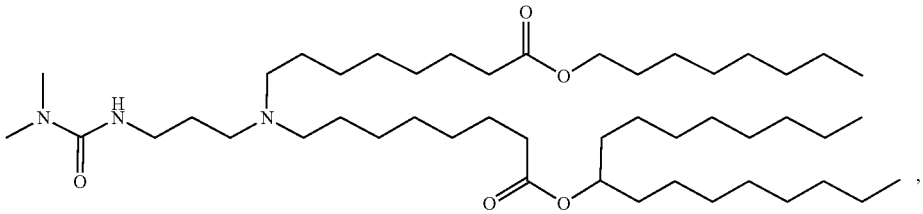

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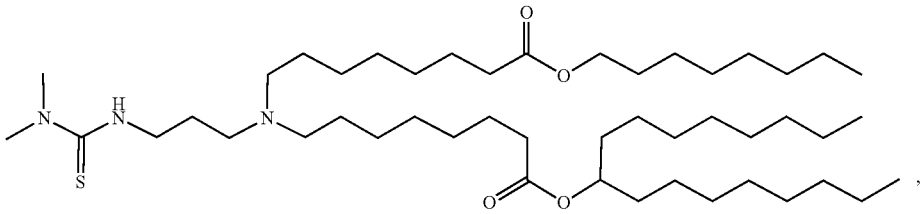

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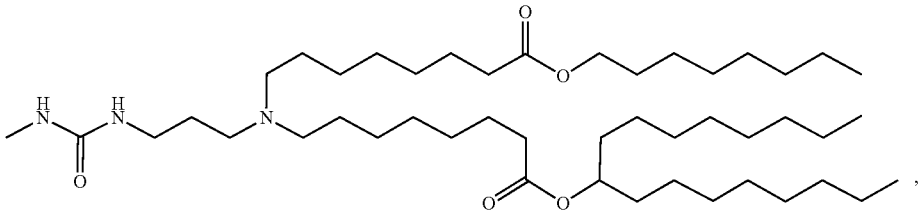

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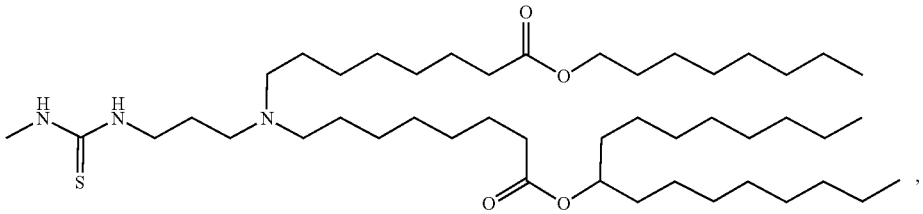

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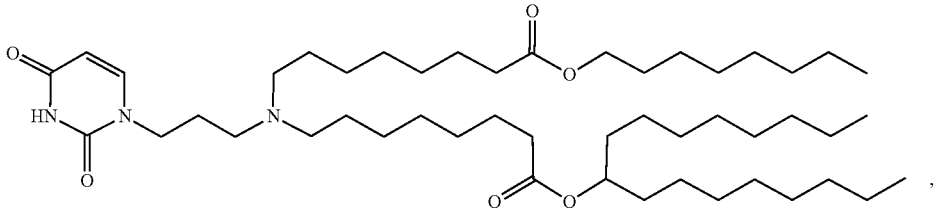

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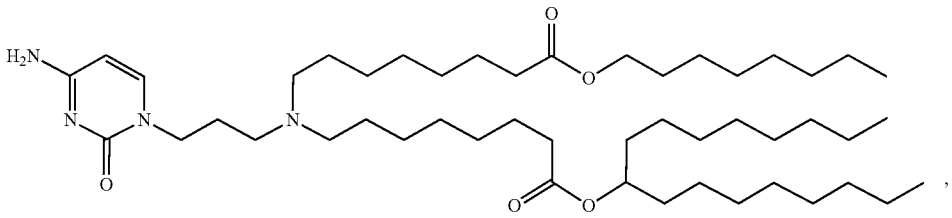

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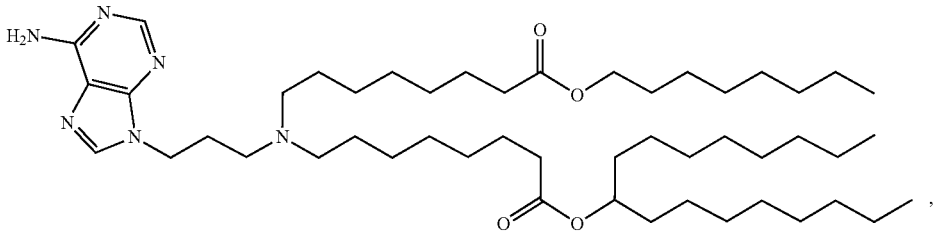

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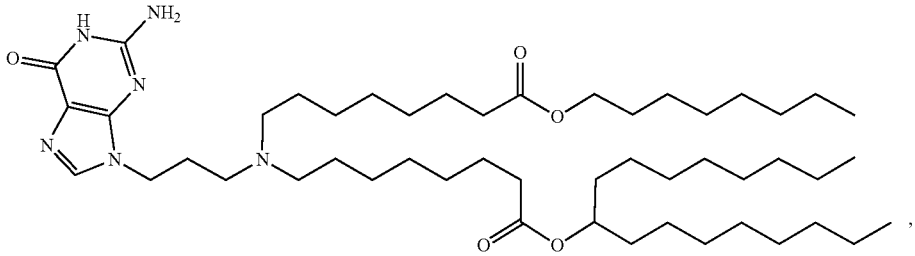

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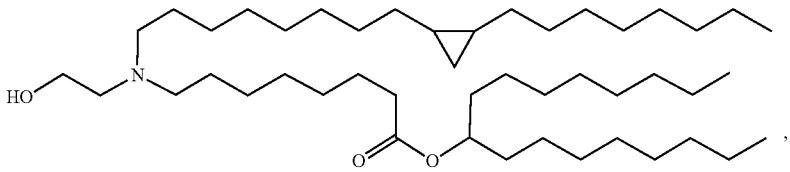

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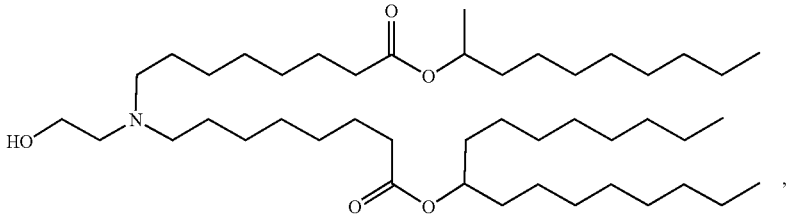

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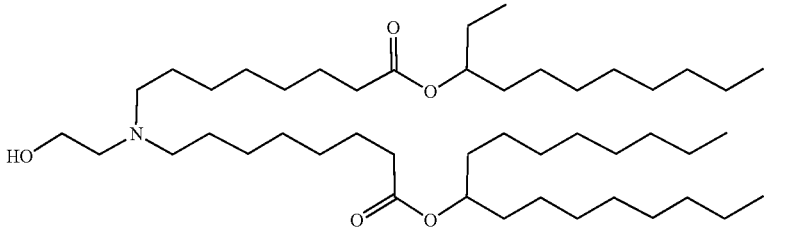

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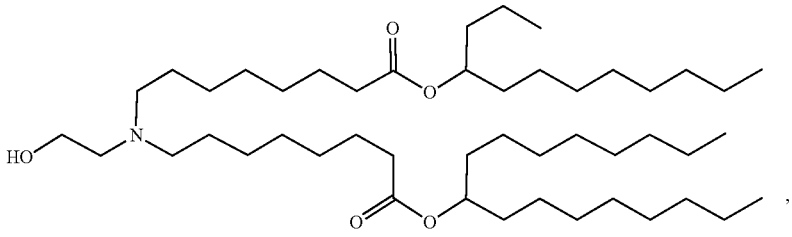

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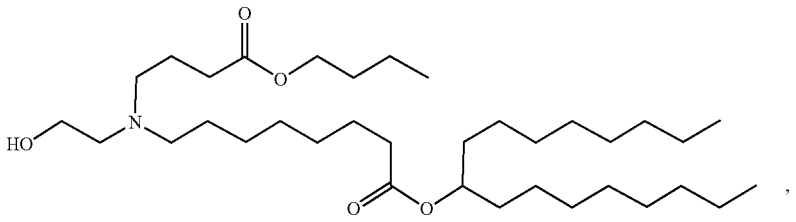

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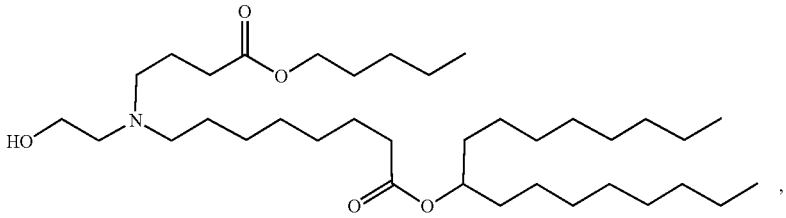

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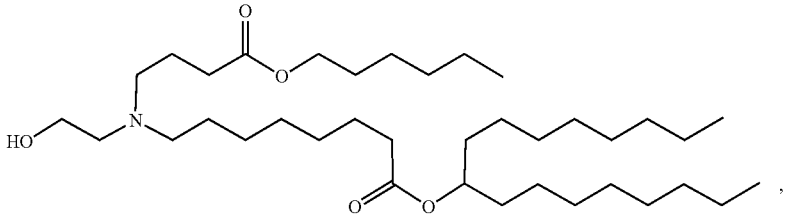

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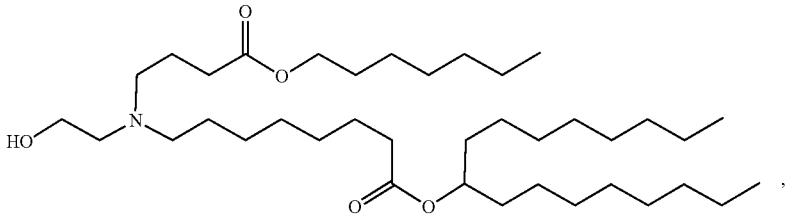

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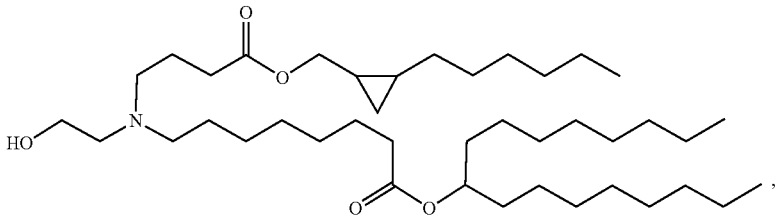

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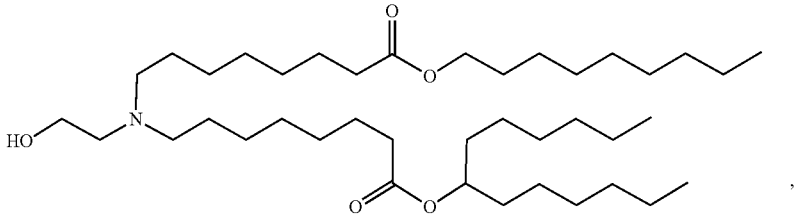
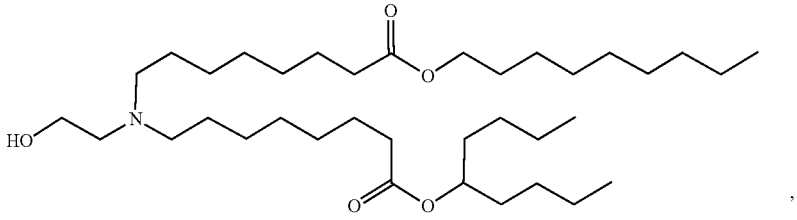


(Compound 57)



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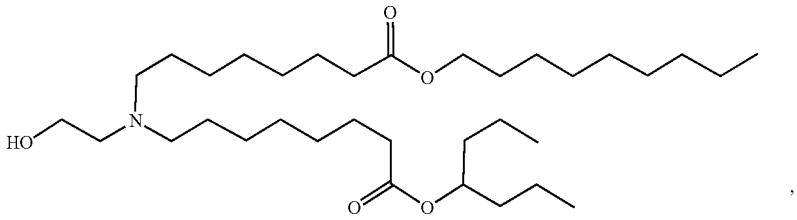
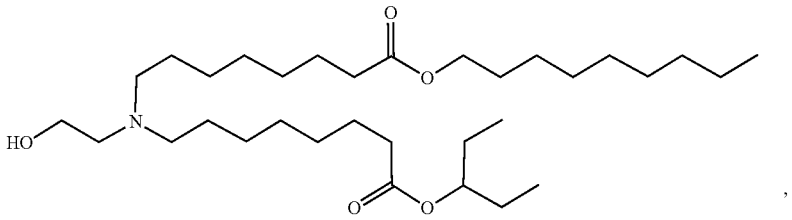
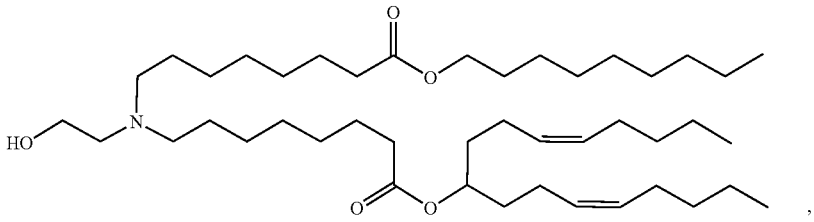
(Compound 58)



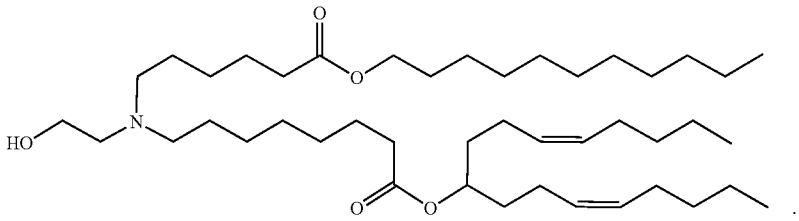
(Compound 59)



(Compound 60)

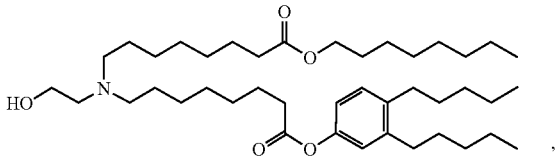


(Compound 61)

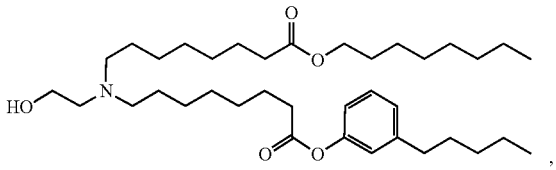


In further embodiments, the compound of Formula (I) is selected from the group consisting of:

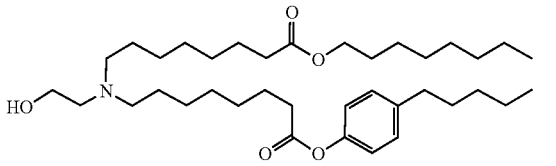
(Compound 62)



(Compound 63)

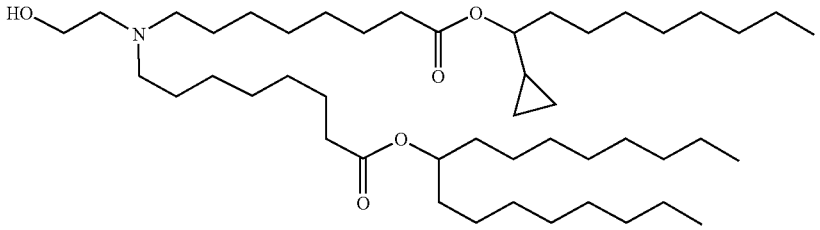


(Compound 64)

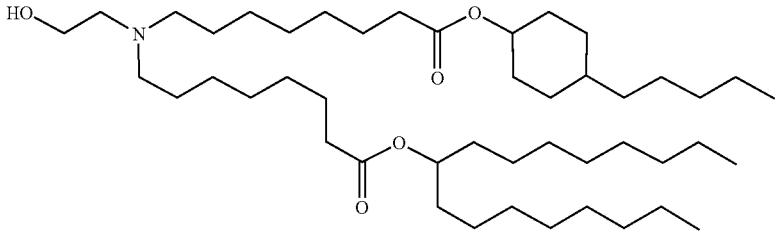


In some embodiments, the compound of Formula (I) is selected from the group consisting of:

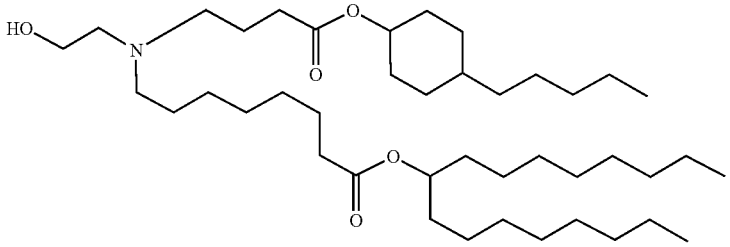
(Compound 65)



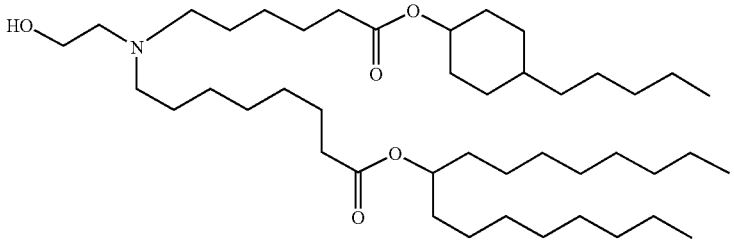
(Compound 66)



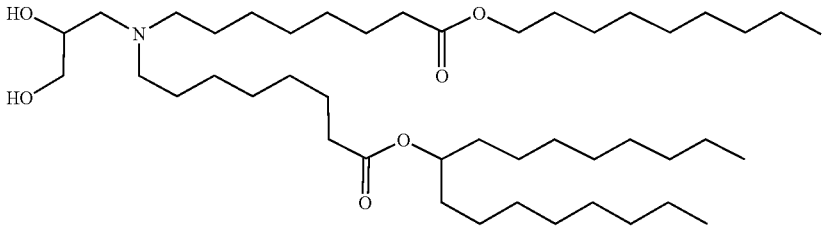
(Compound 67)



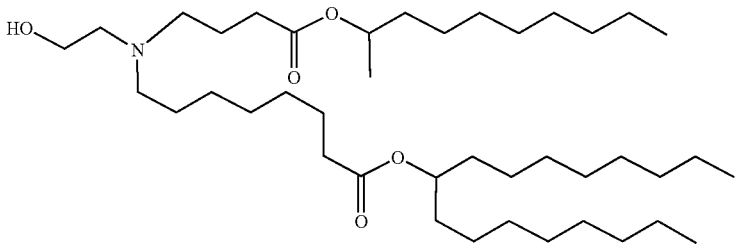
(Compound 68)



(Compound 69)



(Compound 70)



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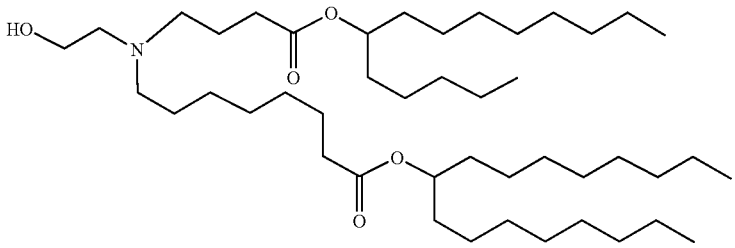
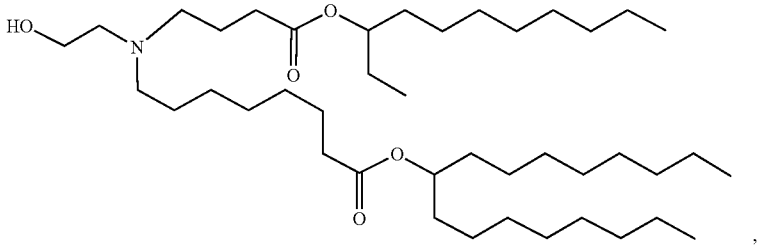
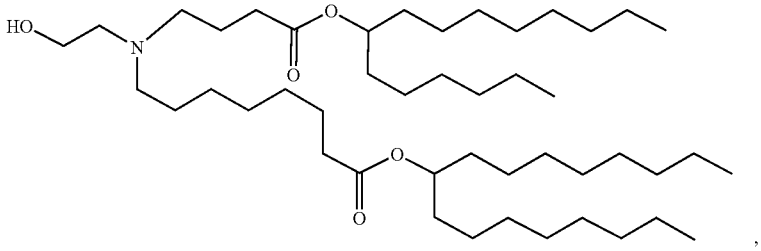
(Compound 71)



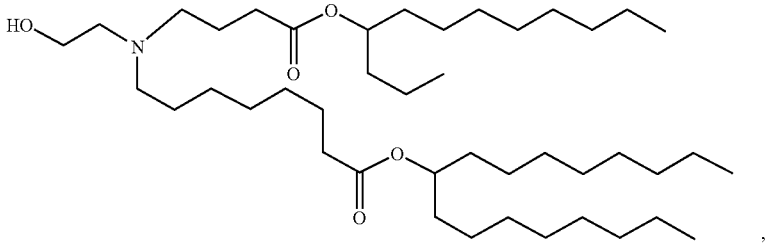
(Compound 72)



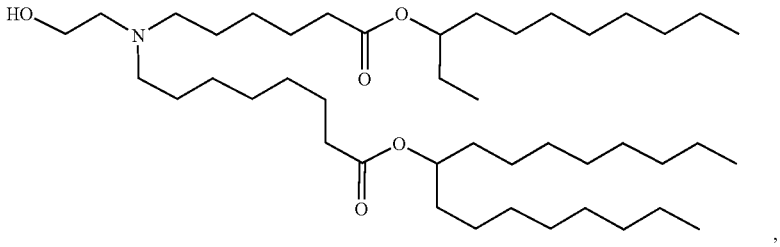
(Compound 73)



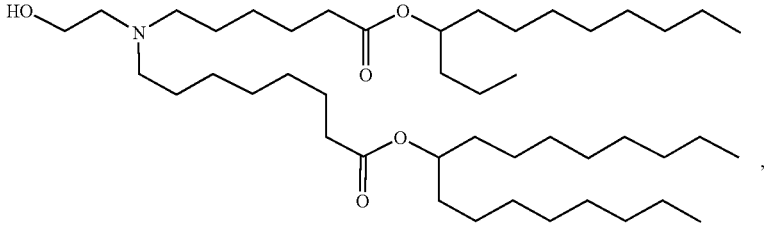
(Compound 74)



(Compound 75)



(Compound 76)



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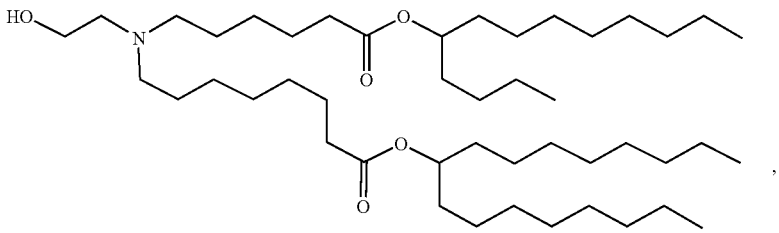
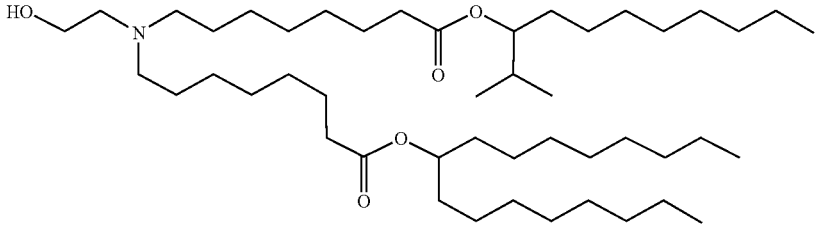
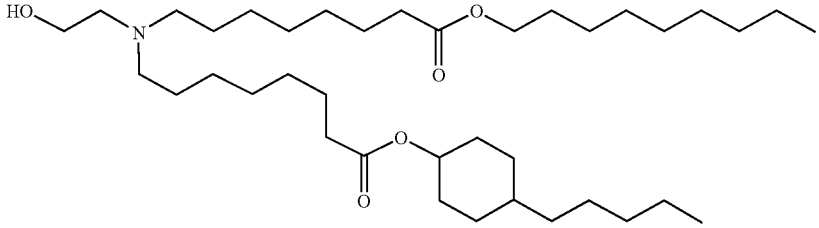
(Compound 77)



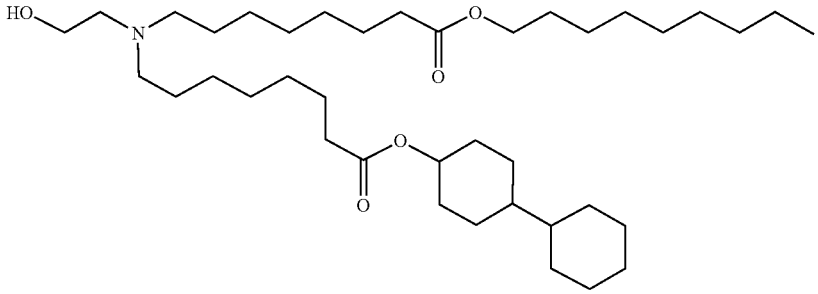
(Compound 78)



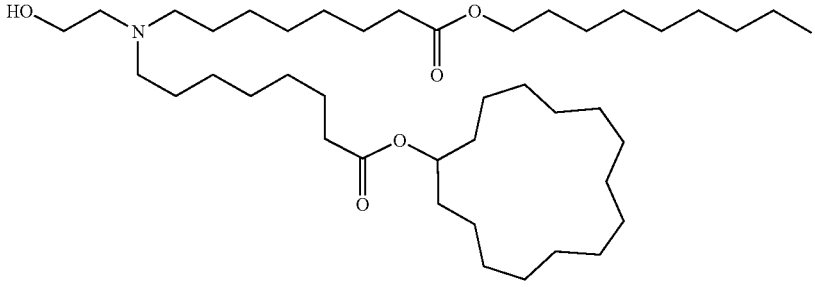
(Compound 79)



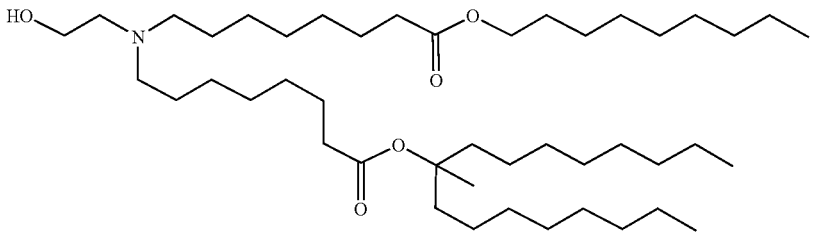
(Compound 80)



(Compound 81)



(Compound 82)



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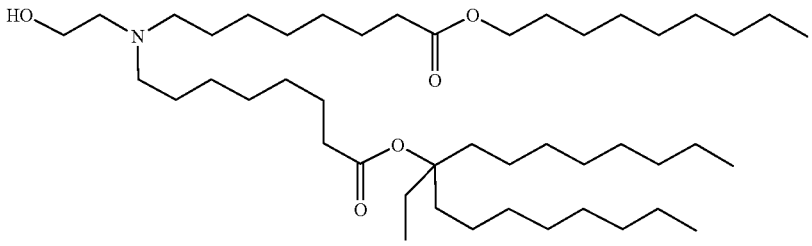
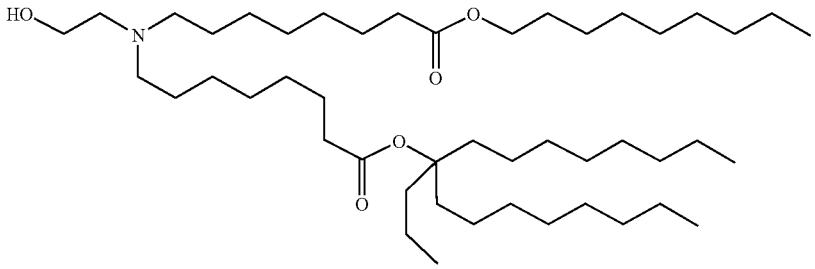
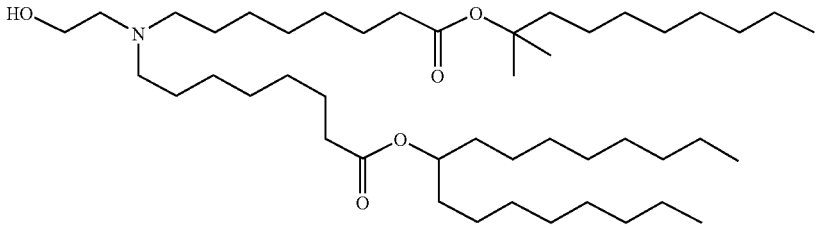
(Compound 83)



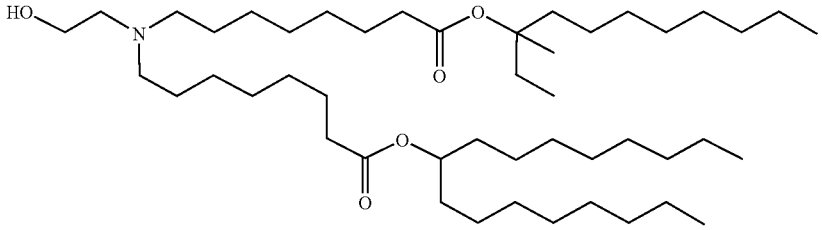
(Compound 84)



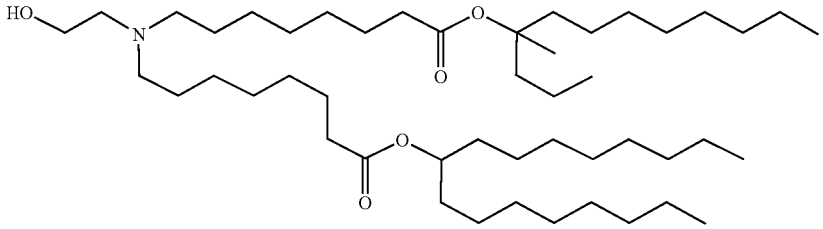
(Compound 85)



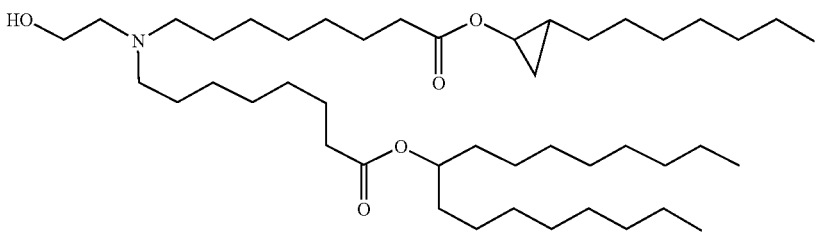
(Compound 86)



(Compound 87)



(Compound 88)



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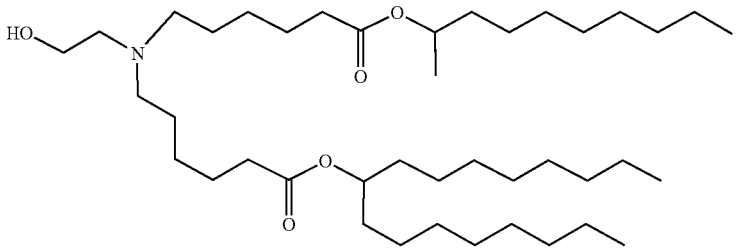
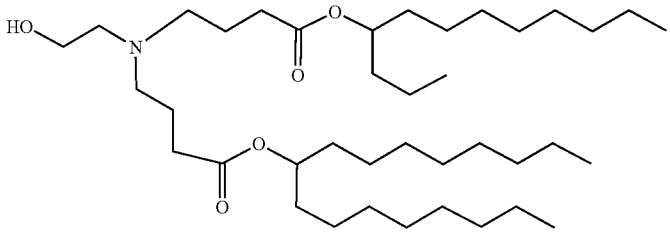
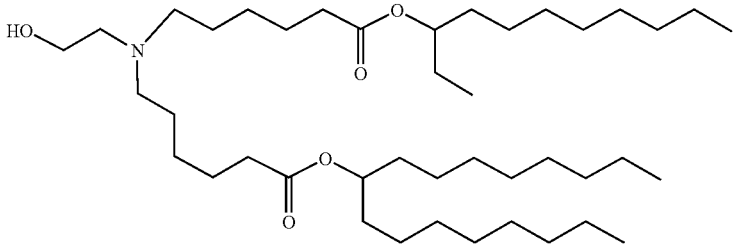
(Compound 89)



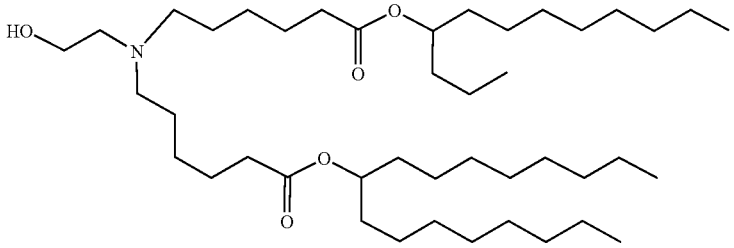
(Compound 90)



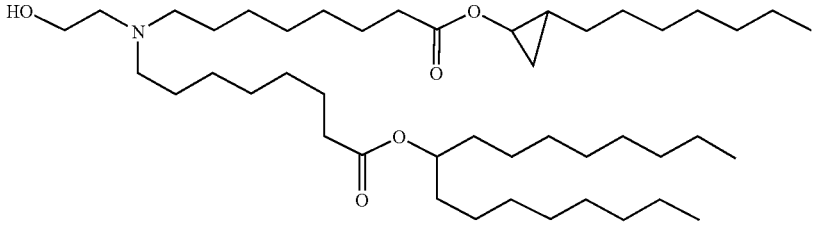
(Compound 91)



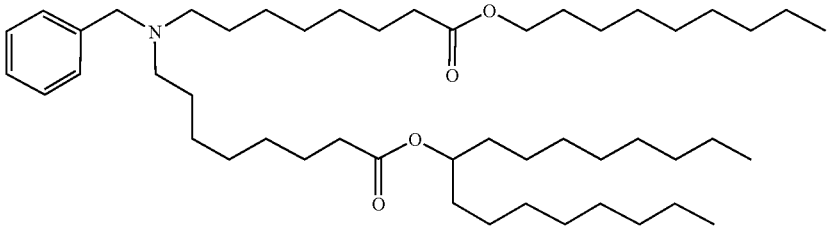
(Compound 92)



(Compound 93)



(Compound 94)



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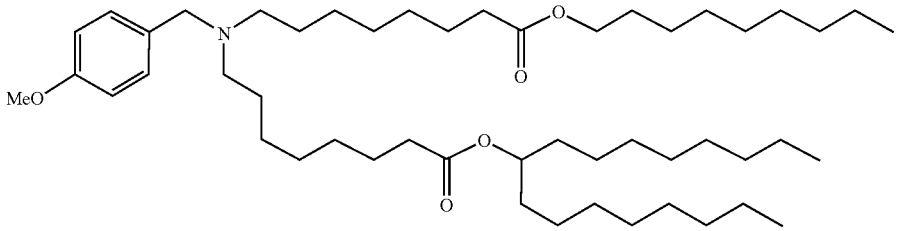
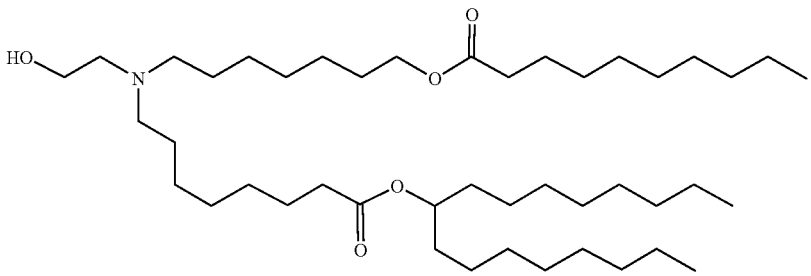
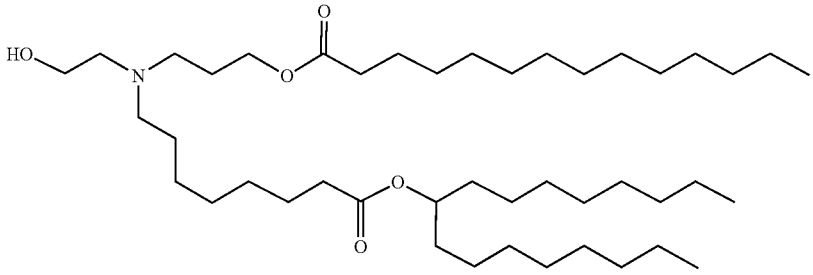
(Compound 95)



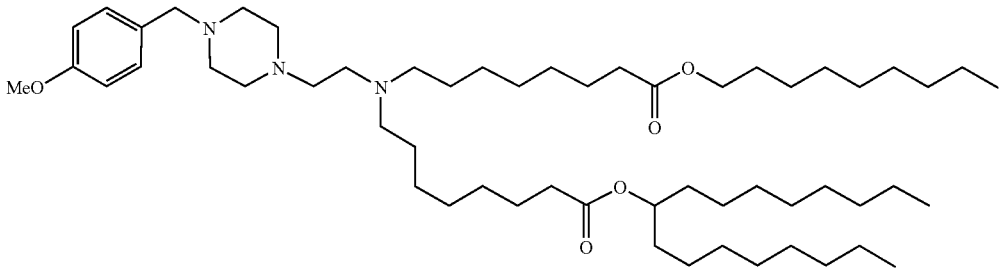
(Compound 96)



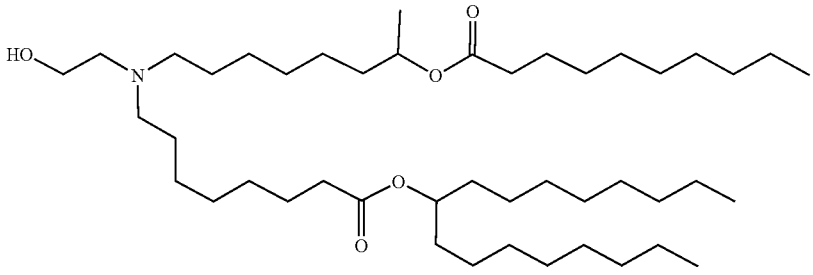
(Compound 97)



(Compound 98)



(Compound 99)



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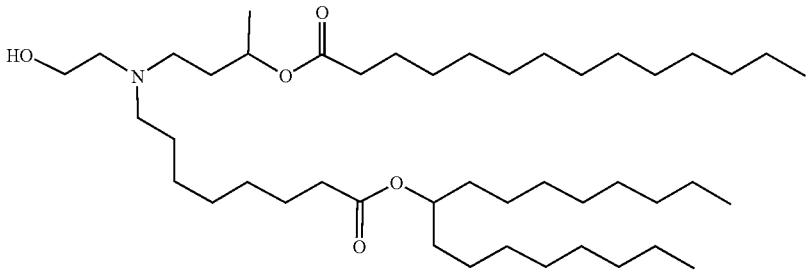
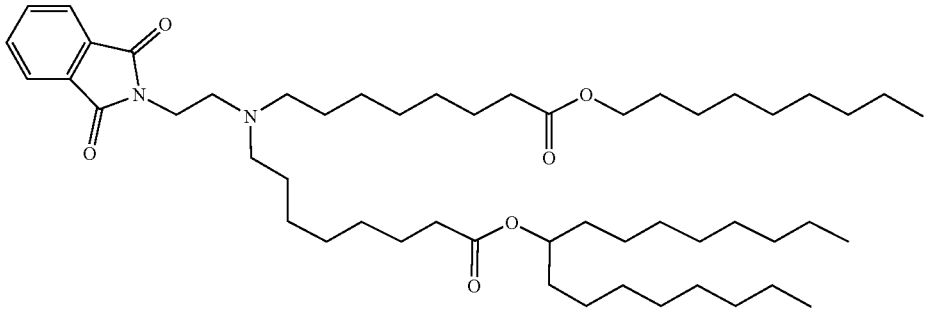
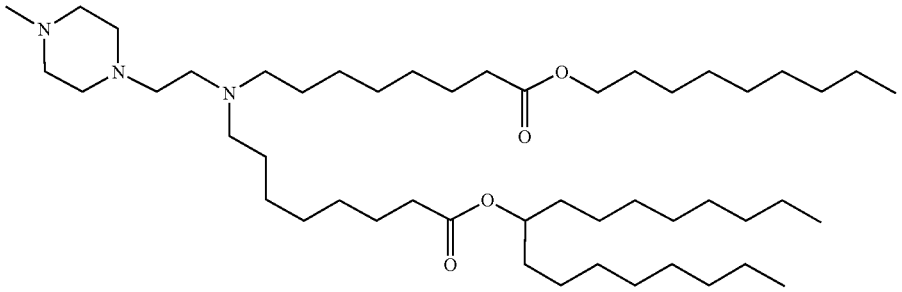
(Compound 100)



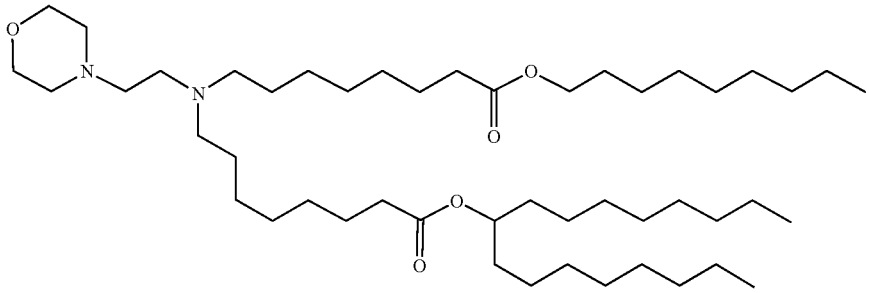
(Compound 101)



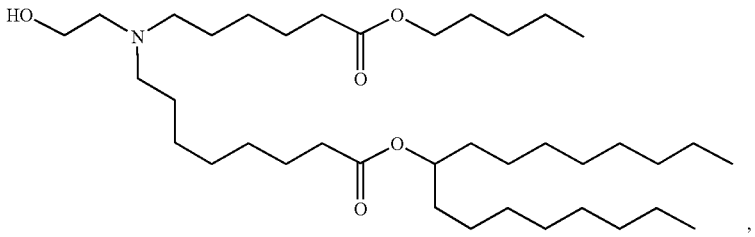
(Compound 102)



(Compound 103)



Compound 104)



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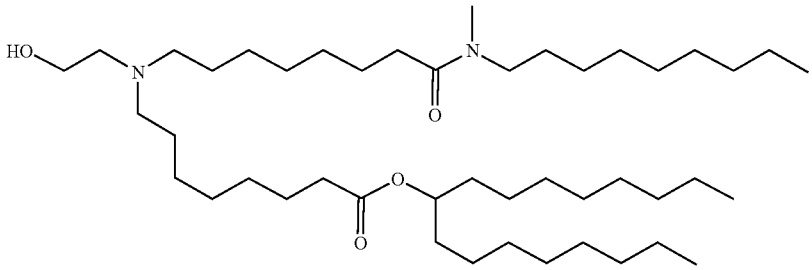
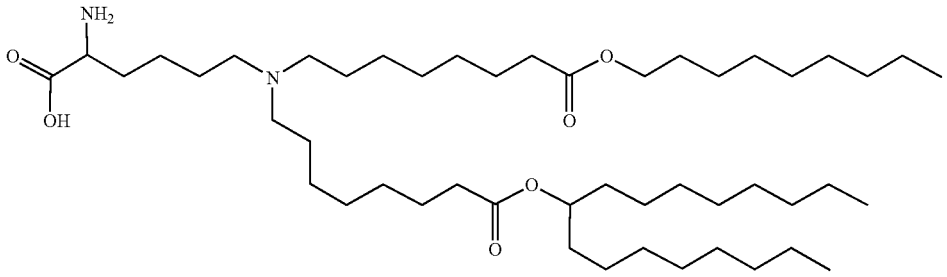
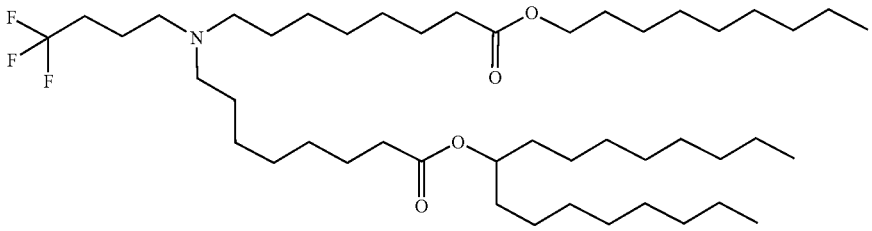
(Compound 105)



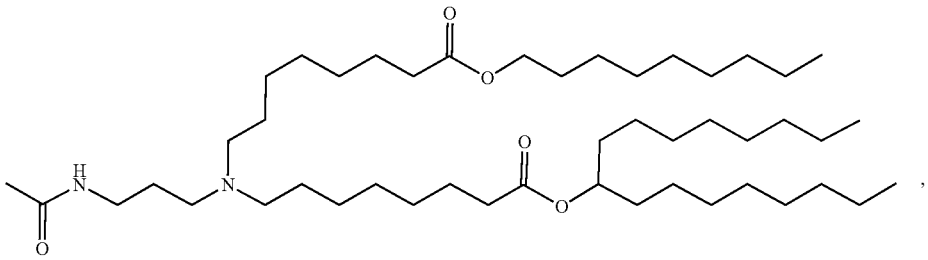
(Compound 106)



(Compound 107)



(Compound 108)



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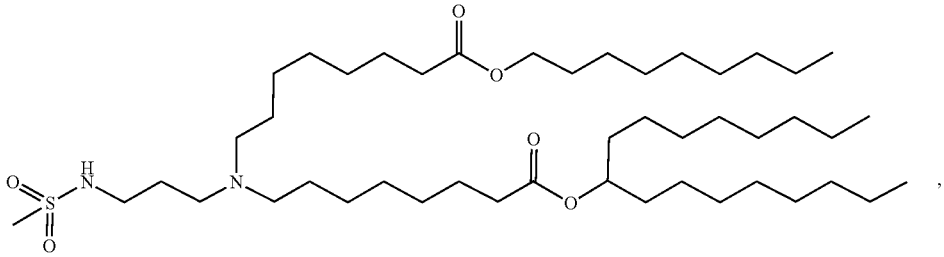

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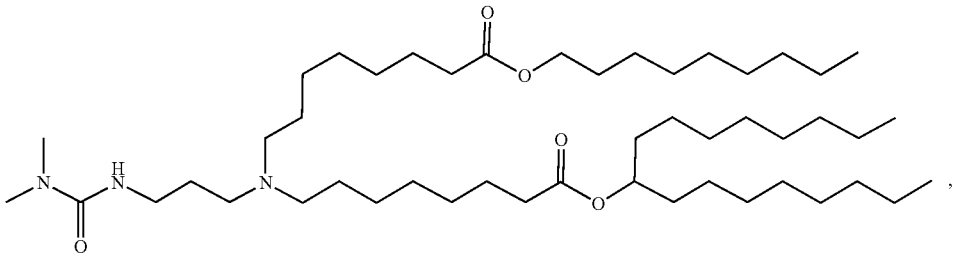

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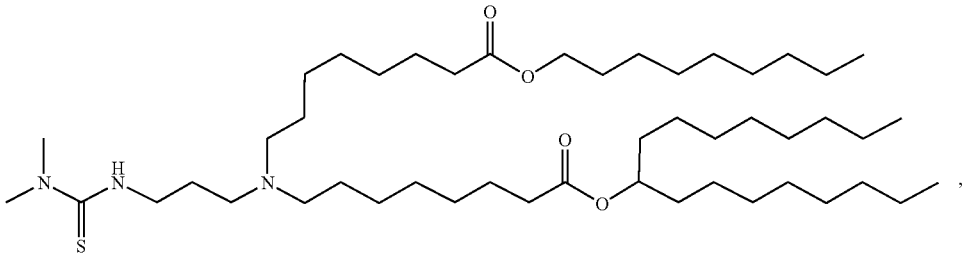
(Compound 111)



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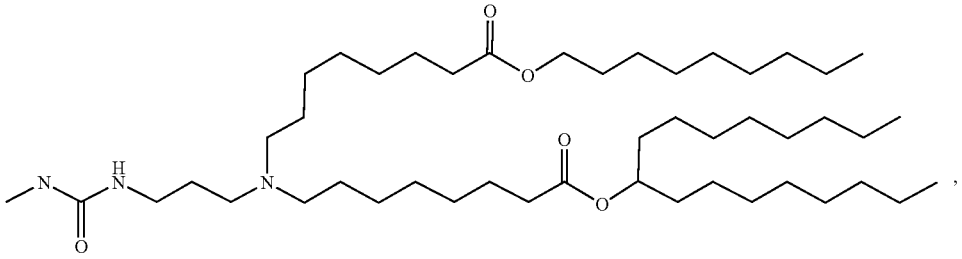

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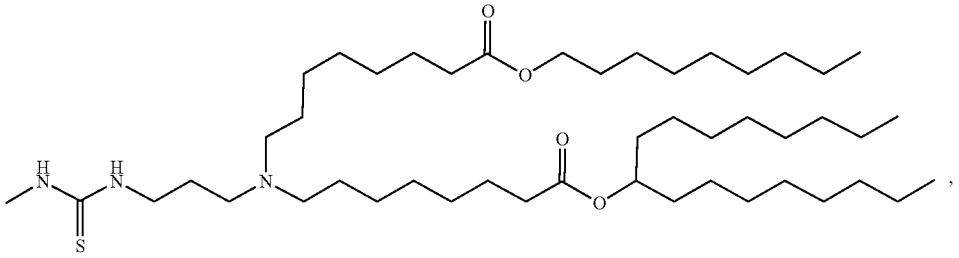

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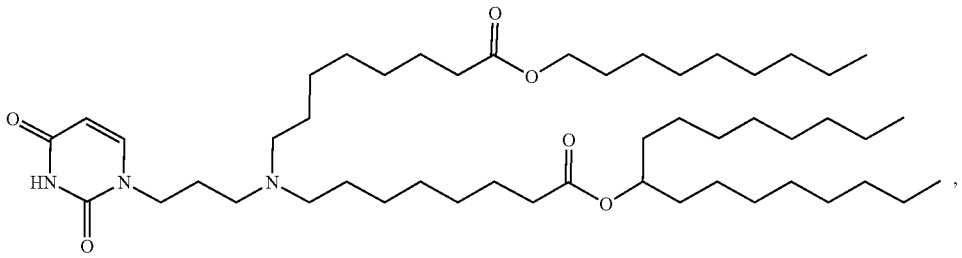

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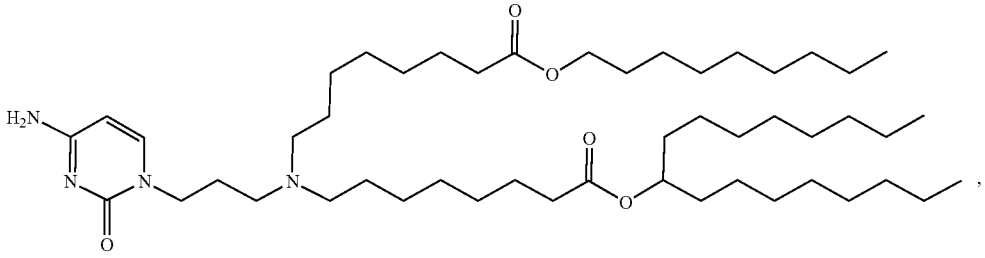

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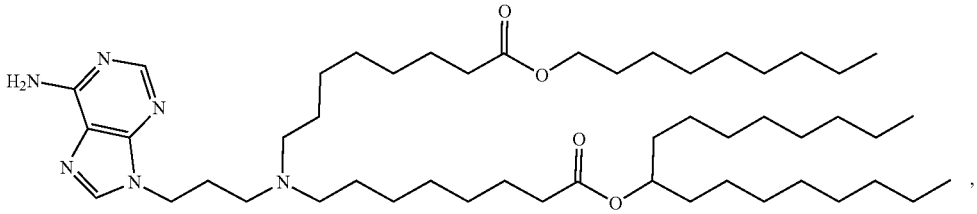

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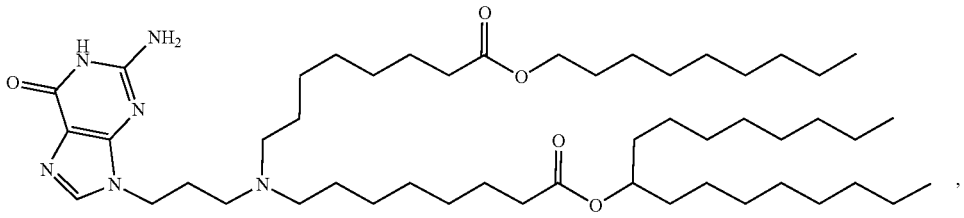
(Compound 117)



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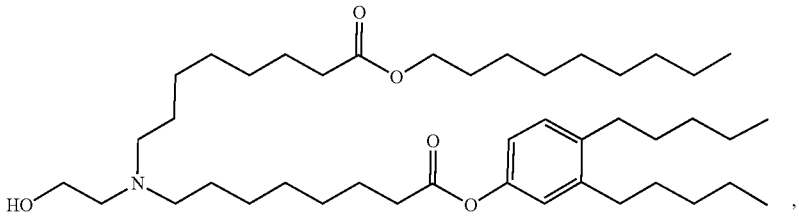

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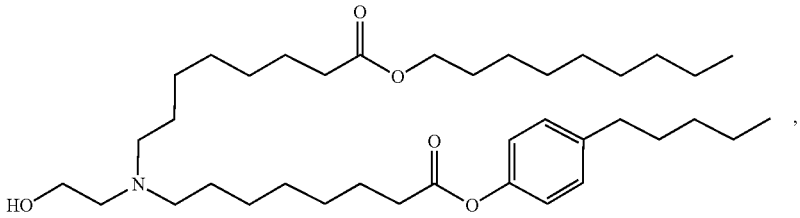

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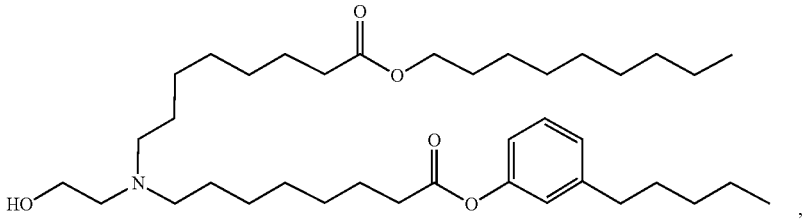

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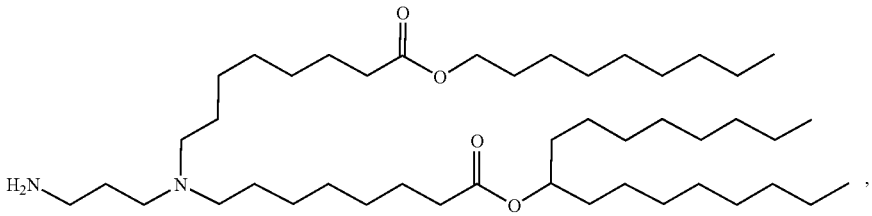

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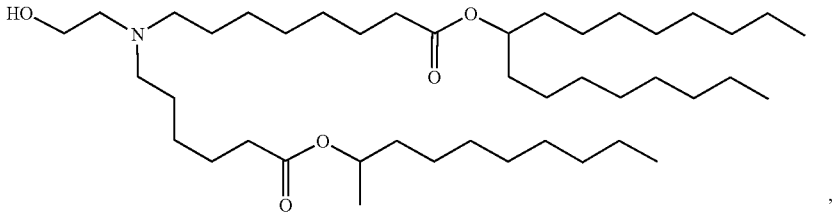

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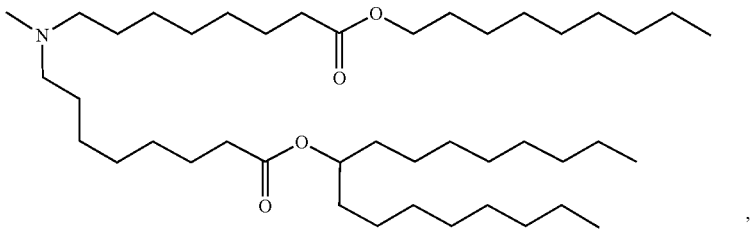

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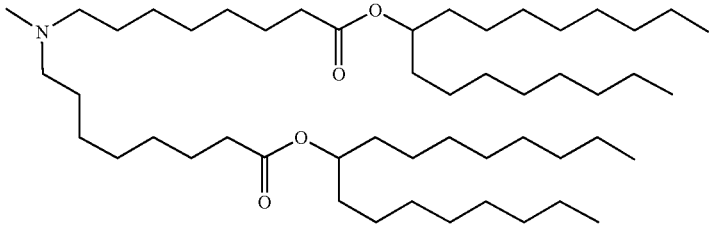

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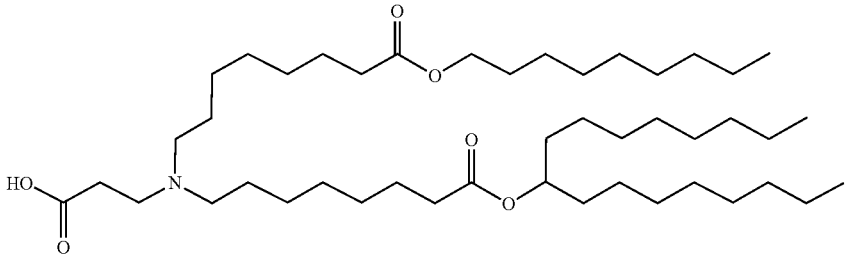

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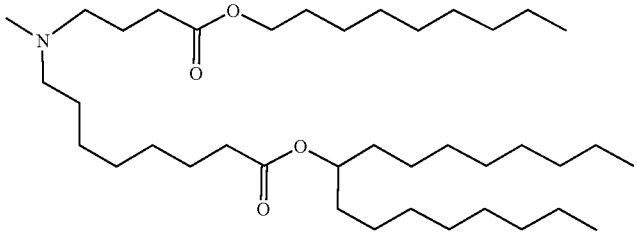

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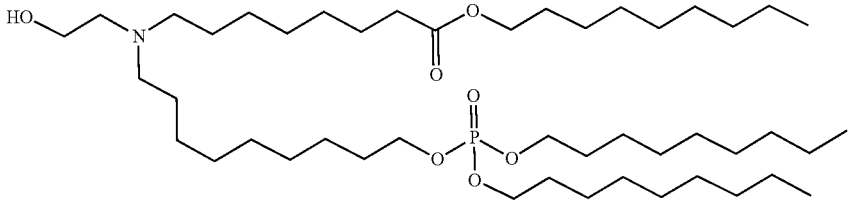

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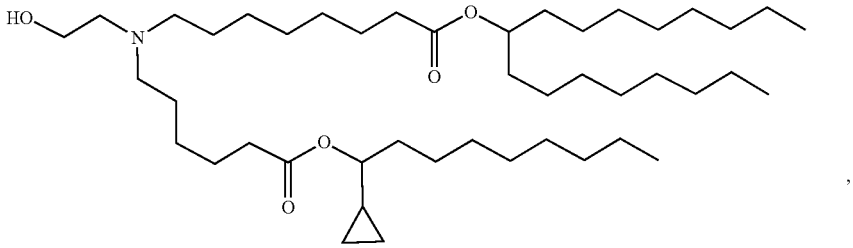

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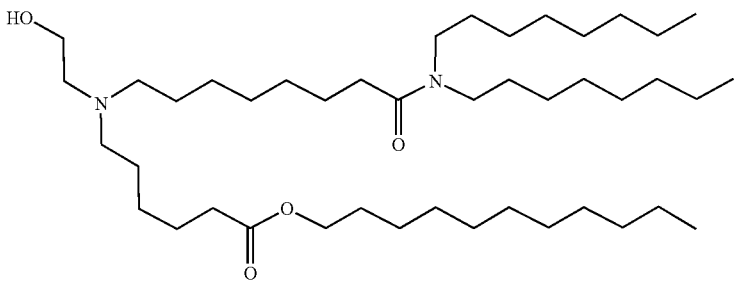

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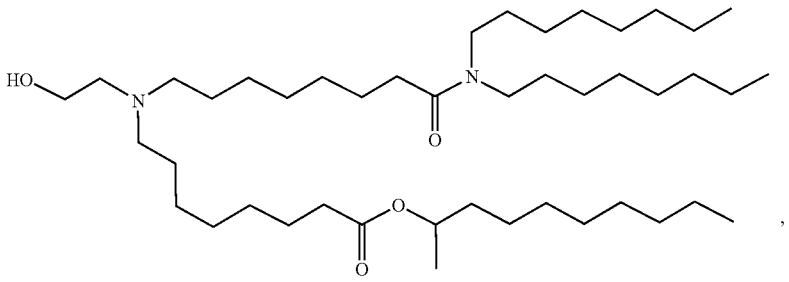

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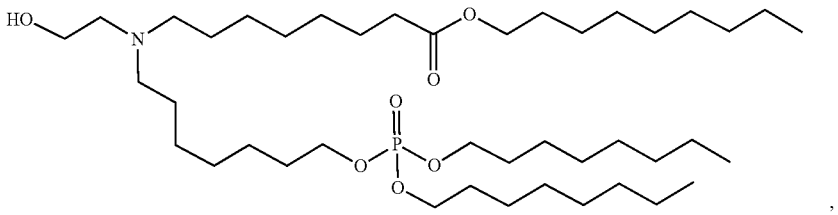

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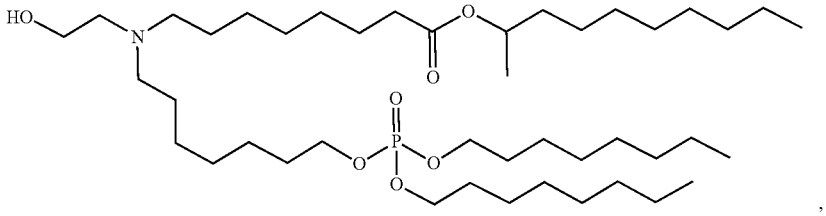

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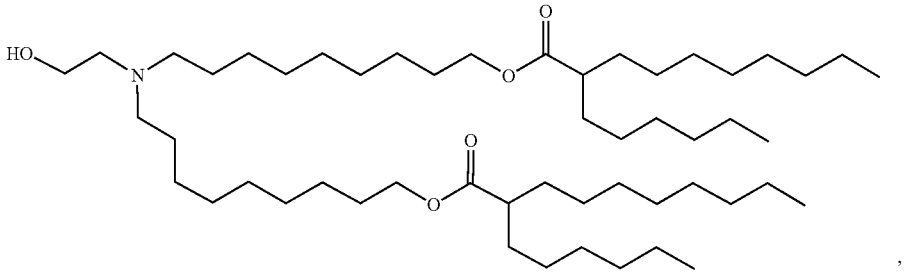

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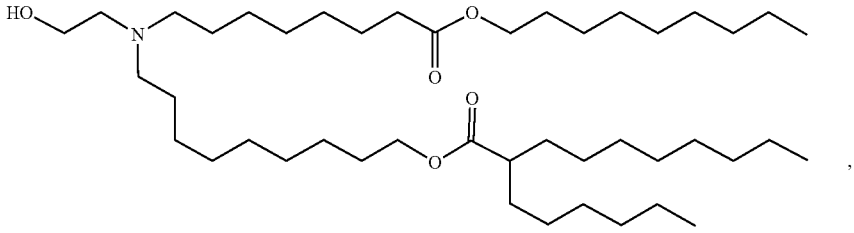

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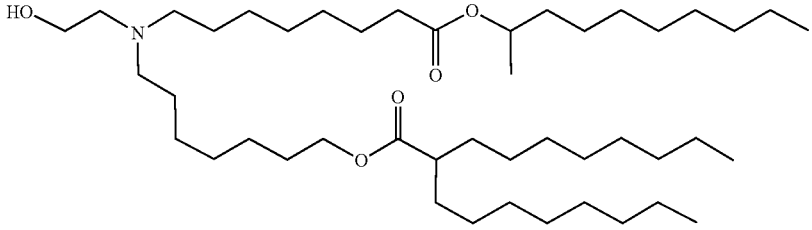

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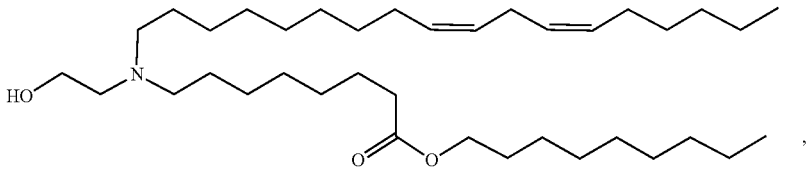
(Compound 136)



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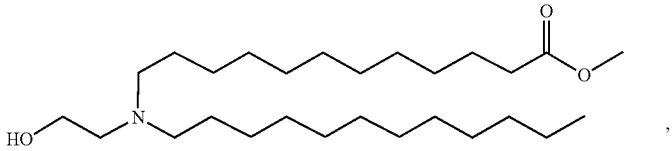

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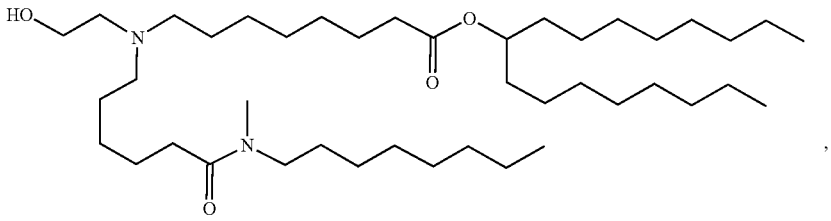

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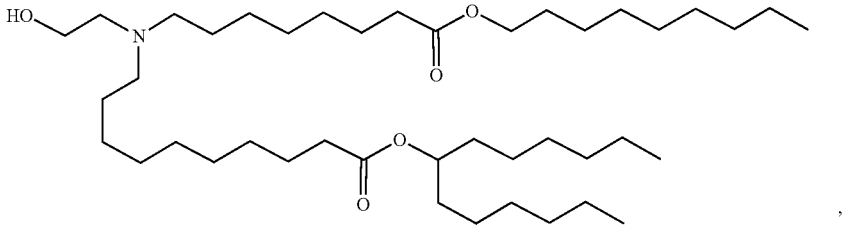

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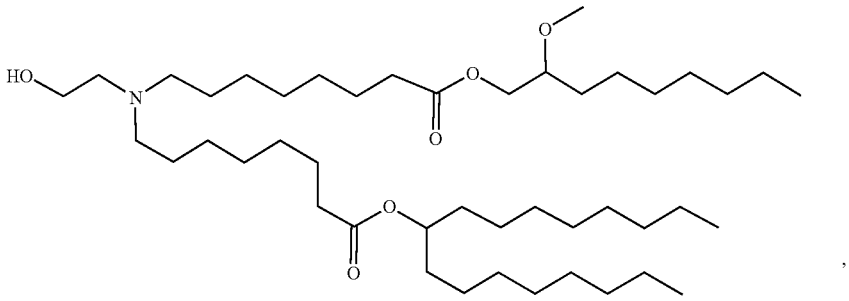

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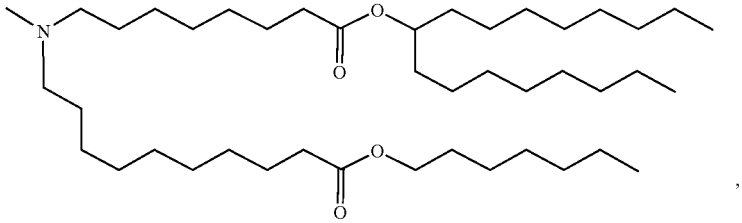

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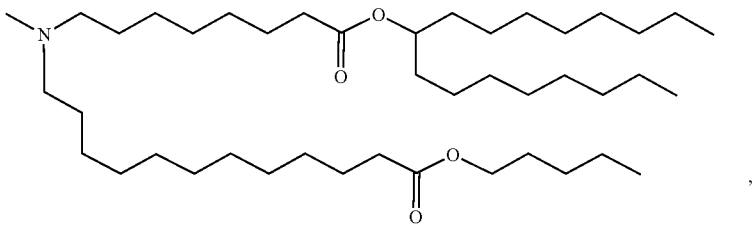

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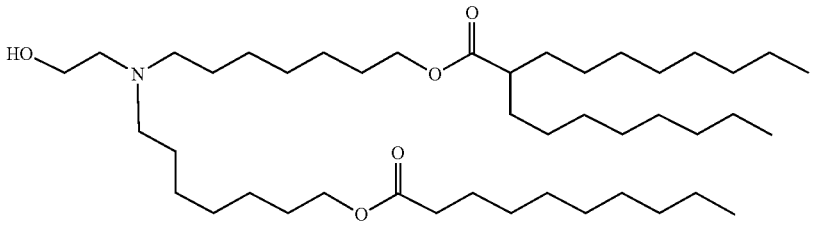

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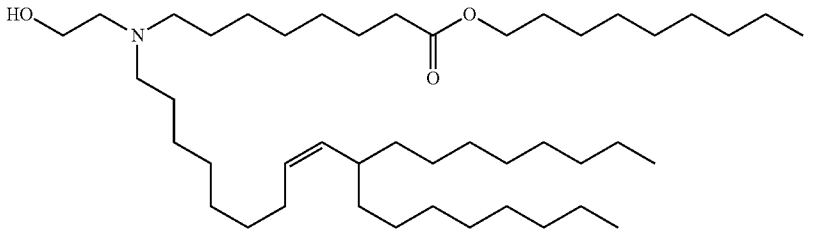

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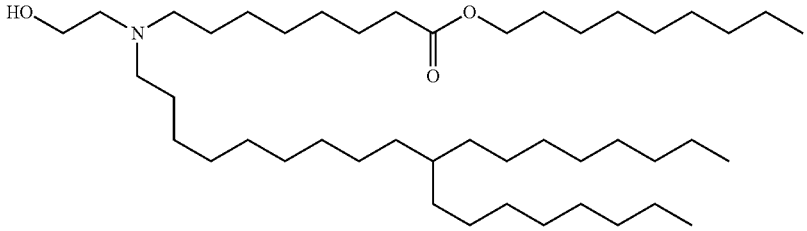

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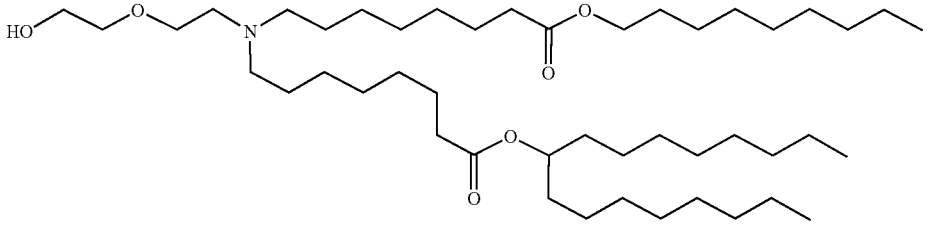

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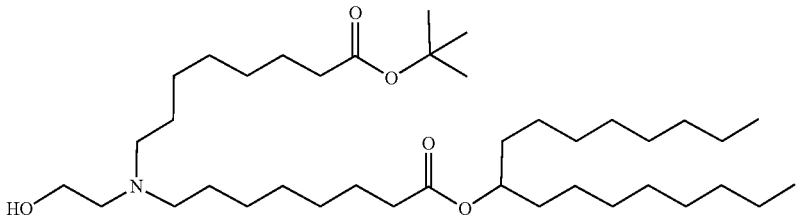

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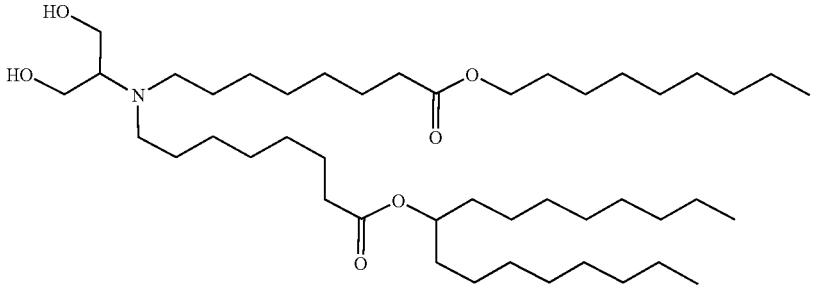

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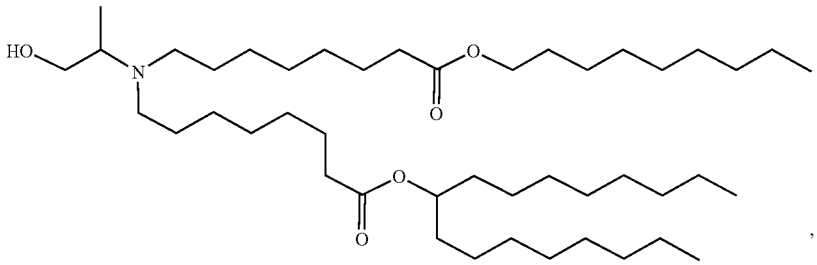
(Compound 157)



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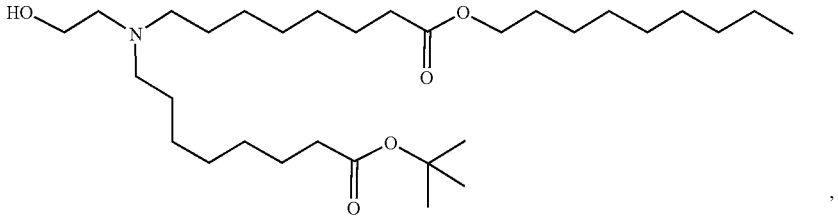

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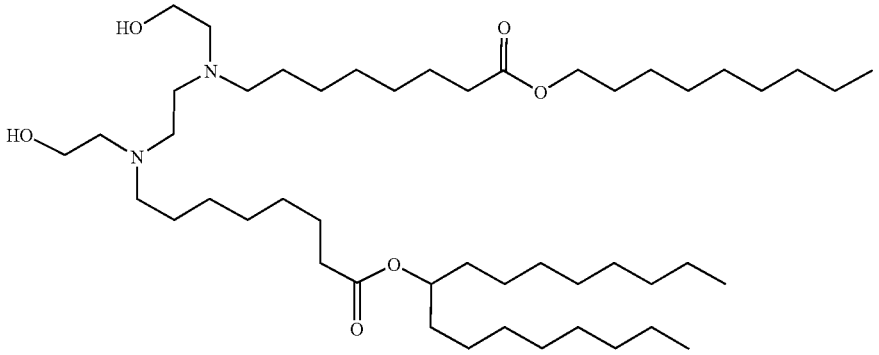

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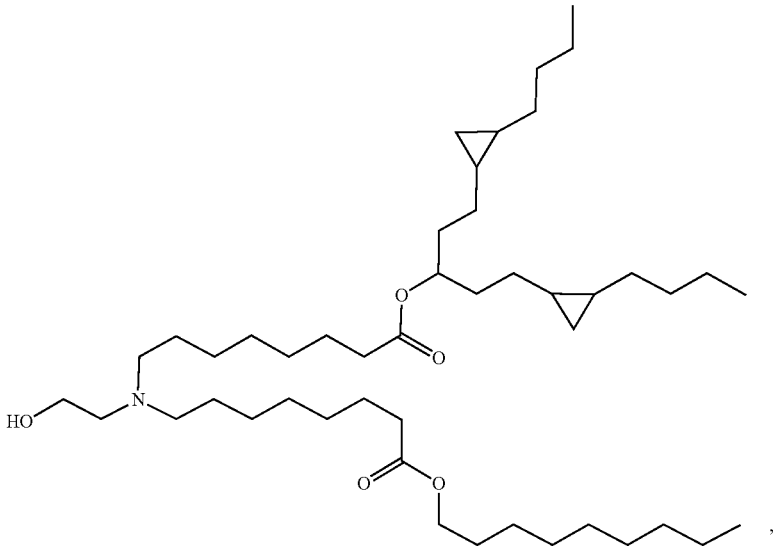

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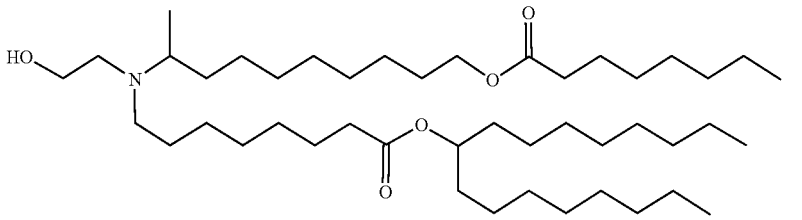
(Compound 161)



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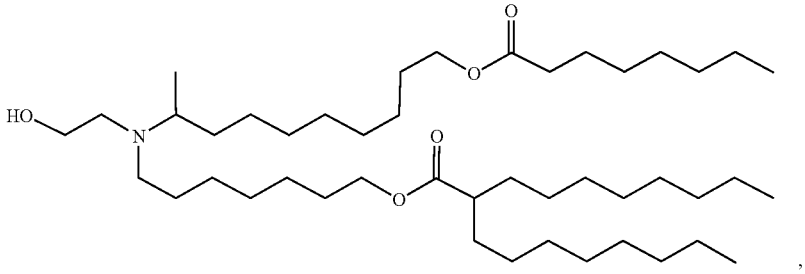
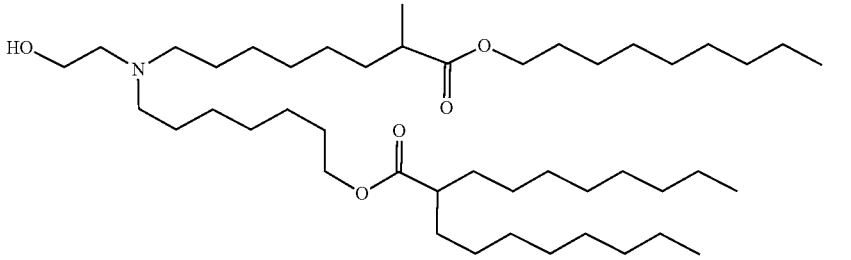


(Compound 163)



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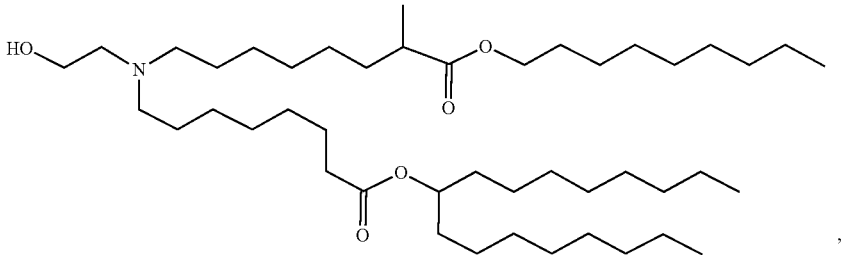

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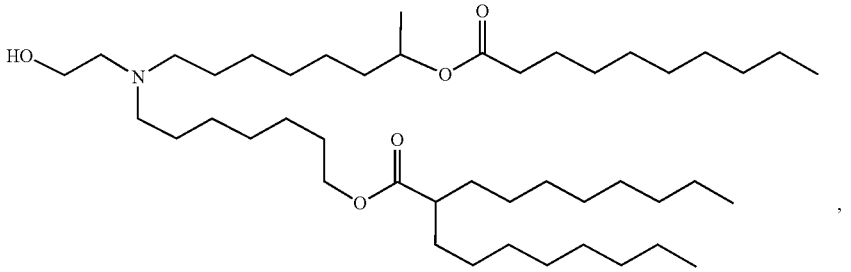

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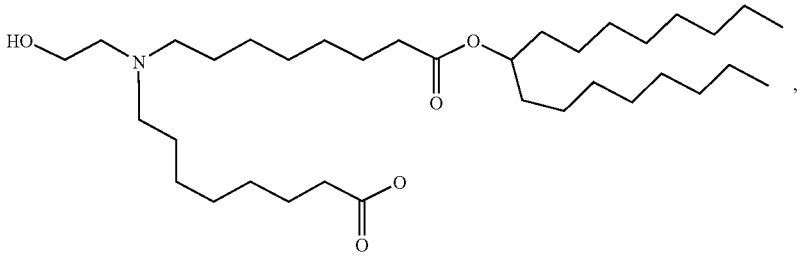

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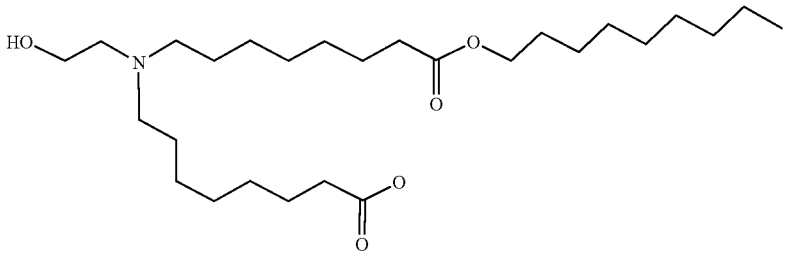

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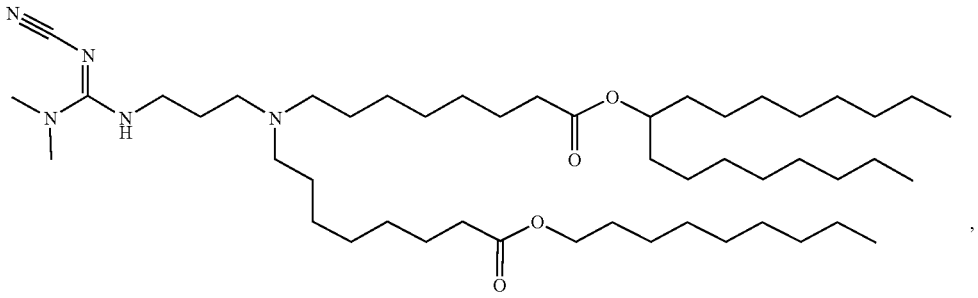

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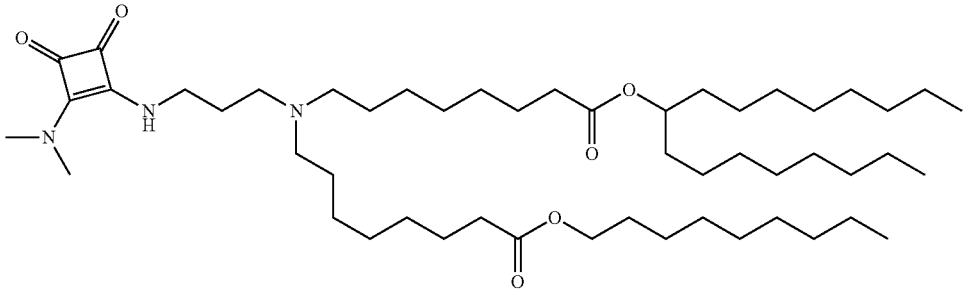

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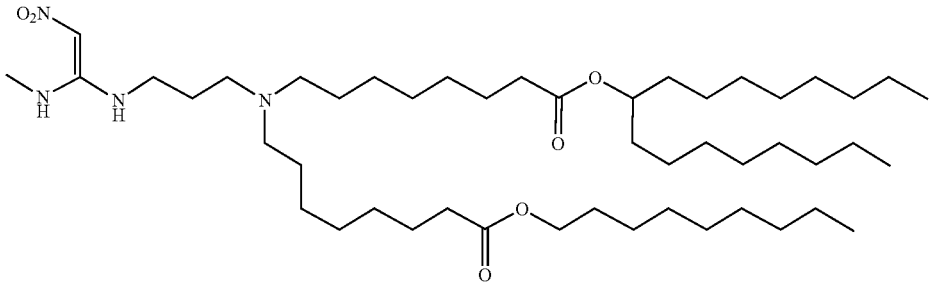

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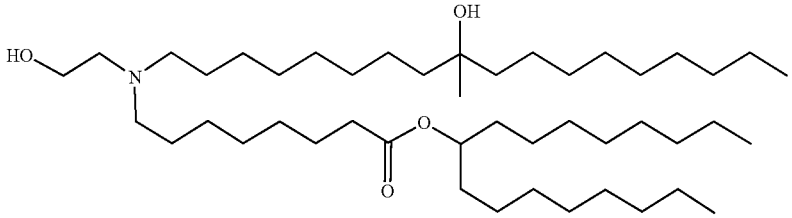

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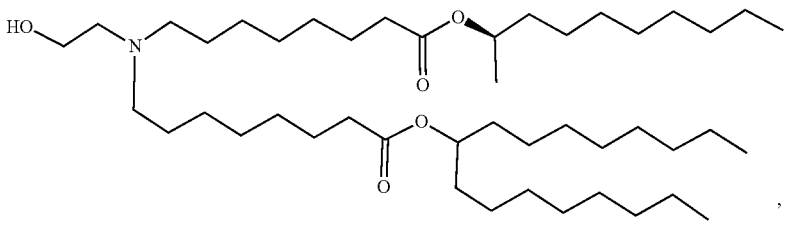

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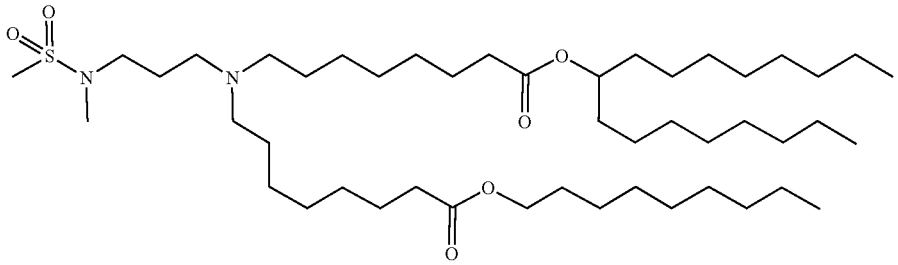

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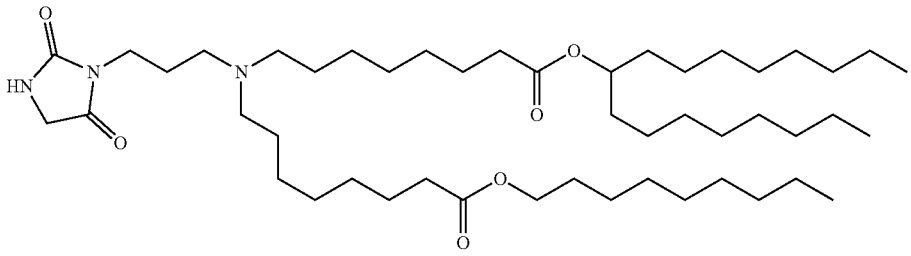

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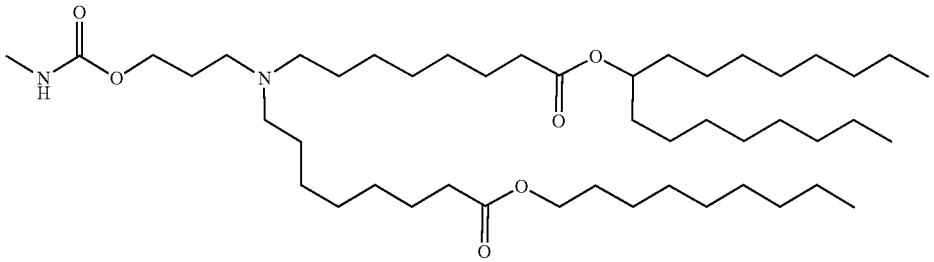

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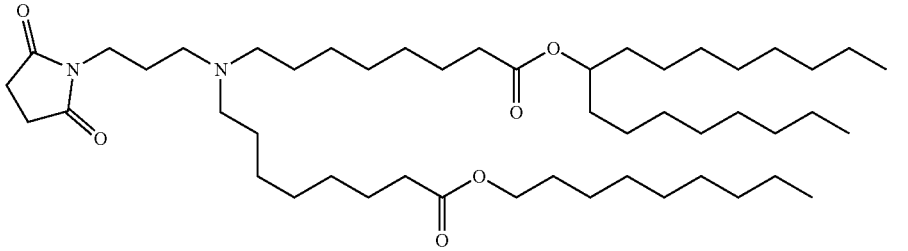

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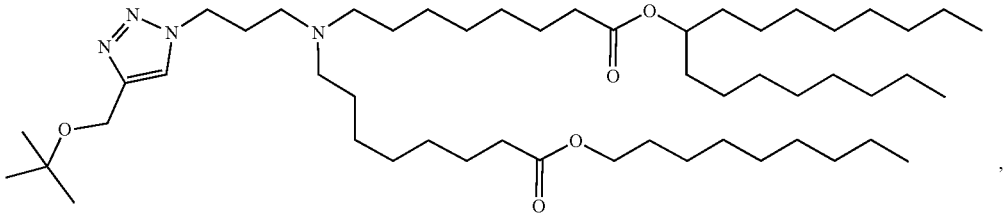

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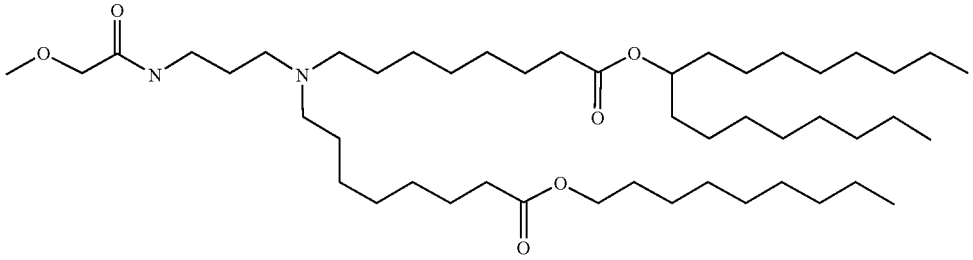

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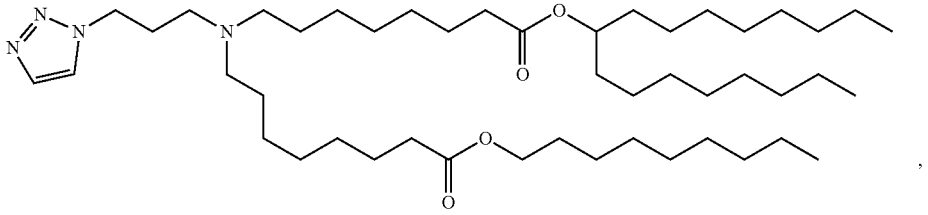

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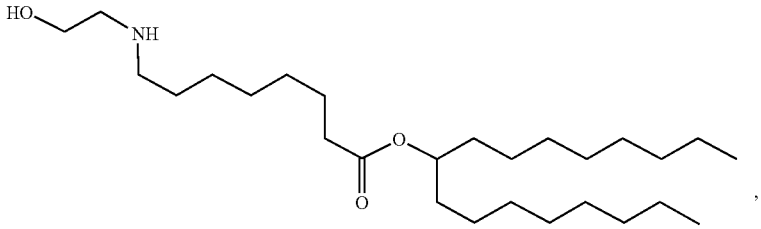

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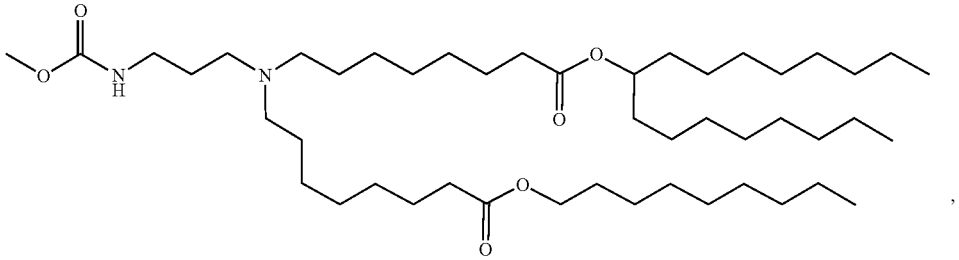

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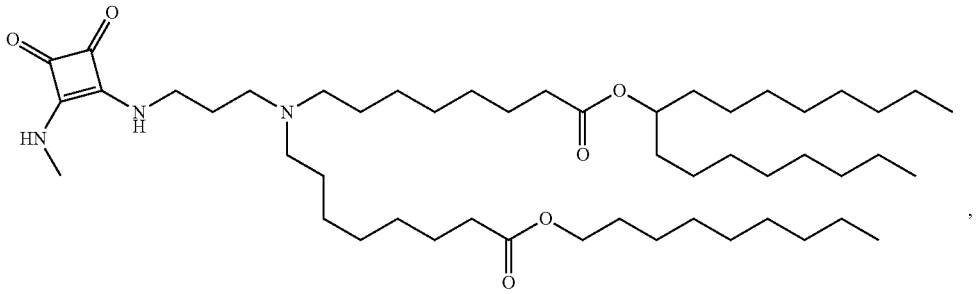

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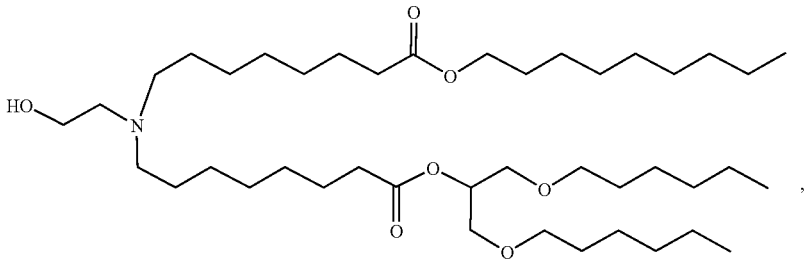

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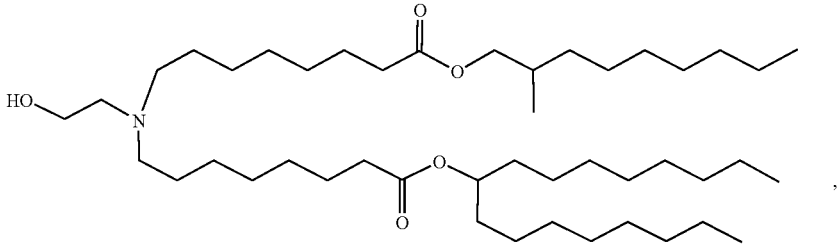

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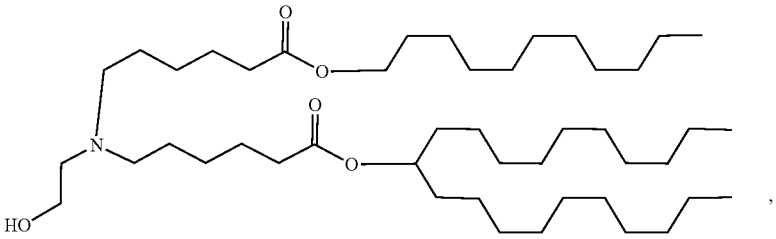

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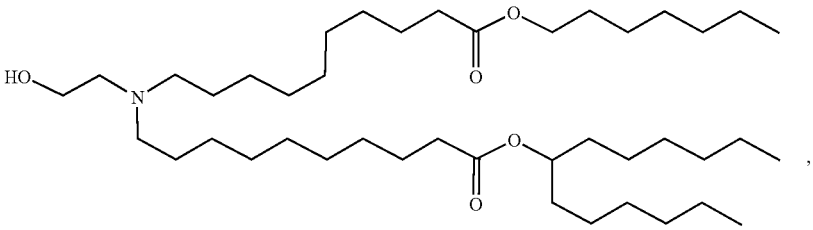

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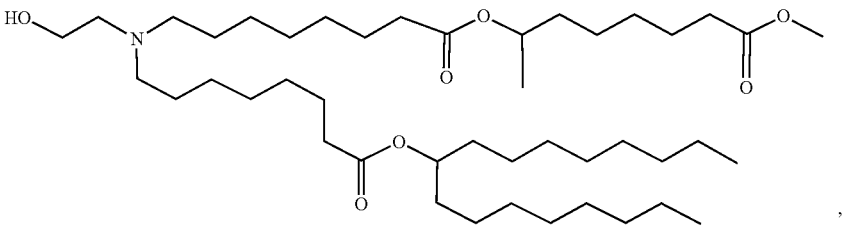

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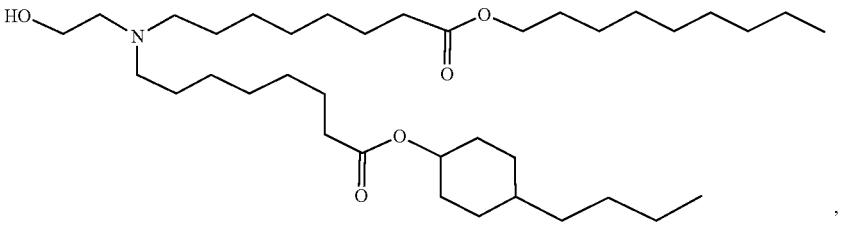

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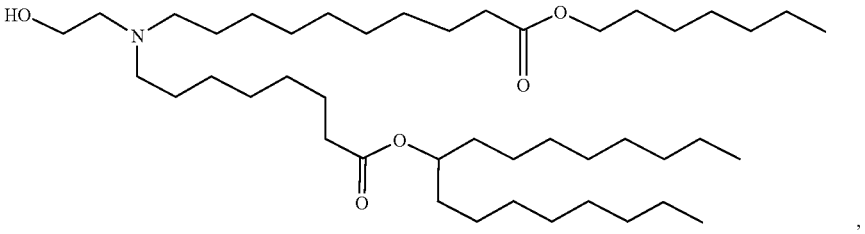

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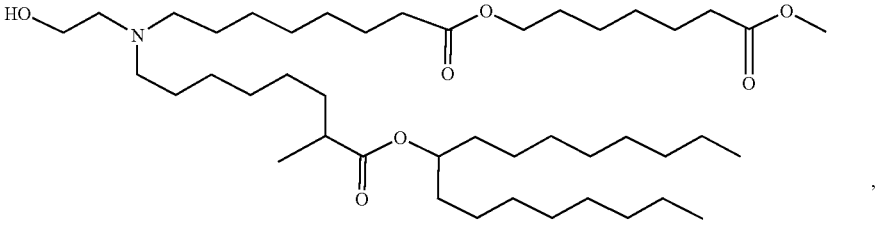

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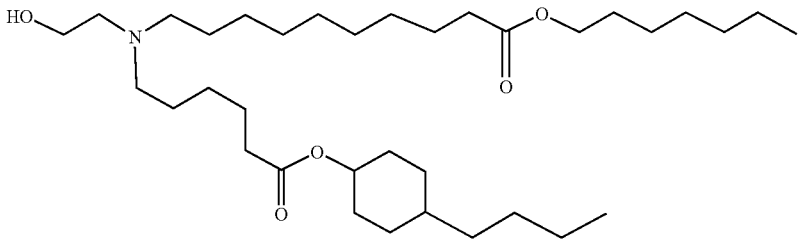

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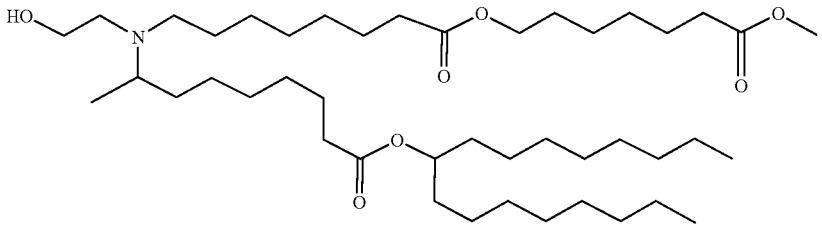

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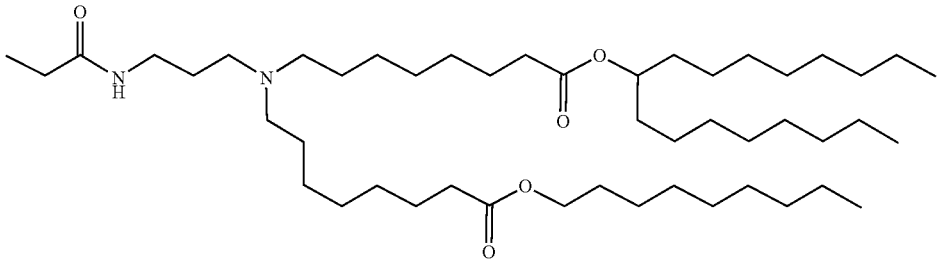

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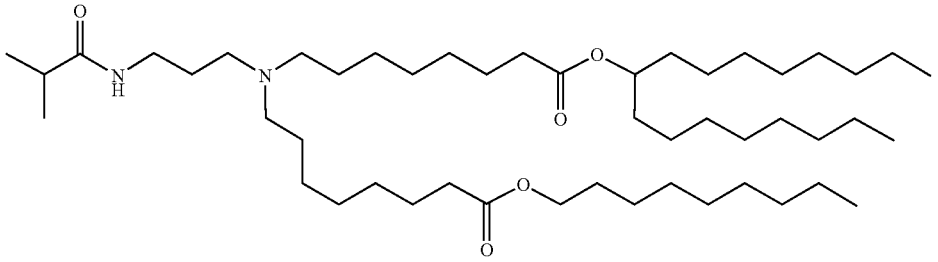

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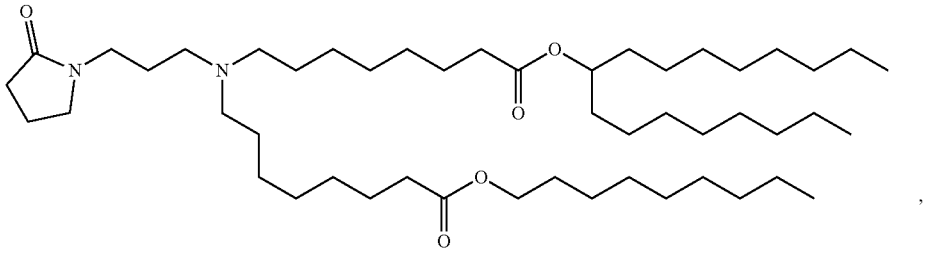

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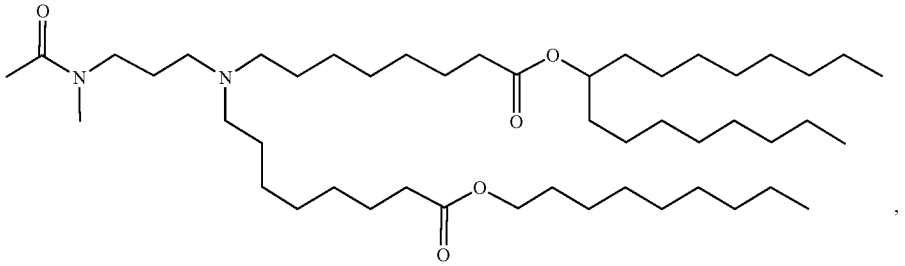

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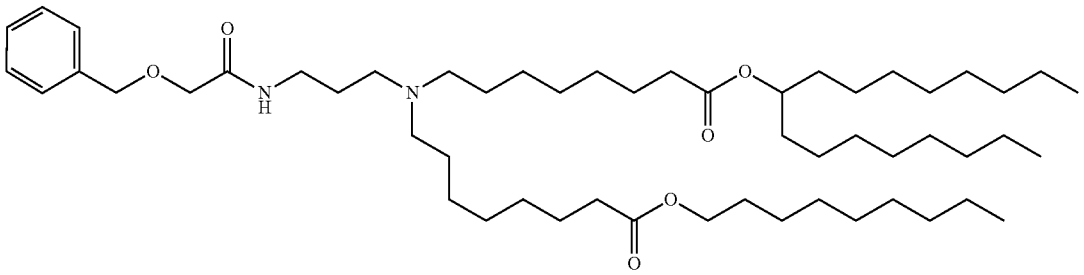
(Compound 197)



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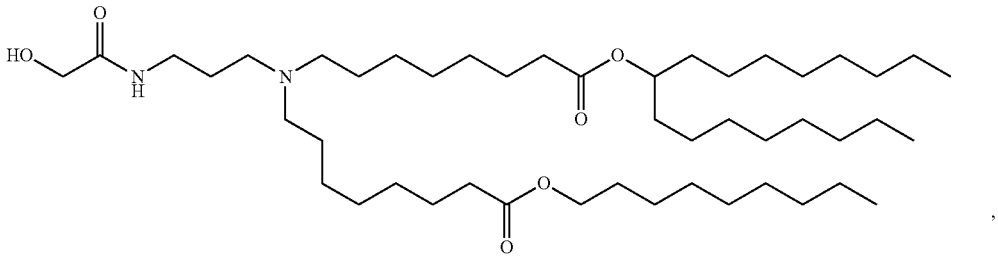

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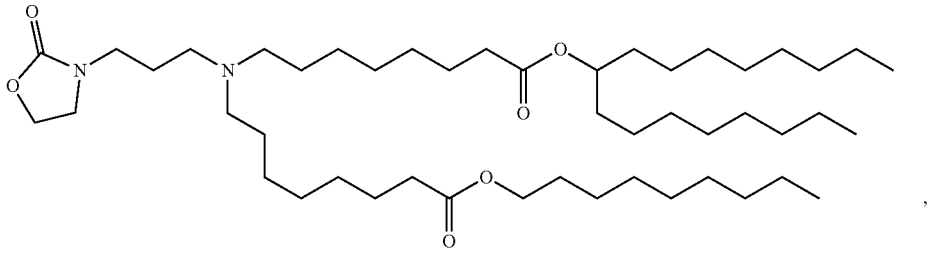

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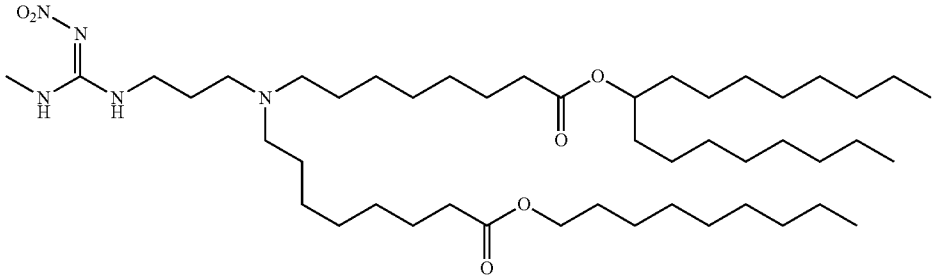

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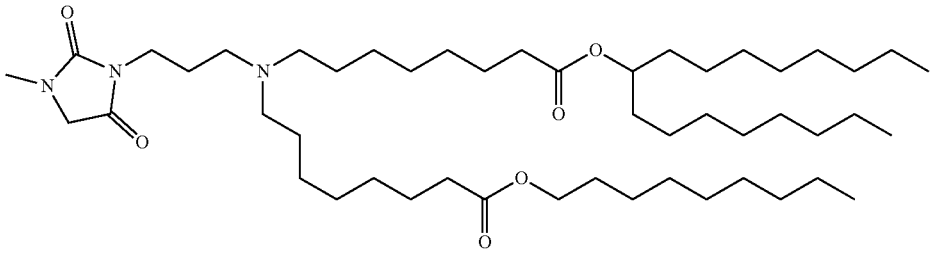

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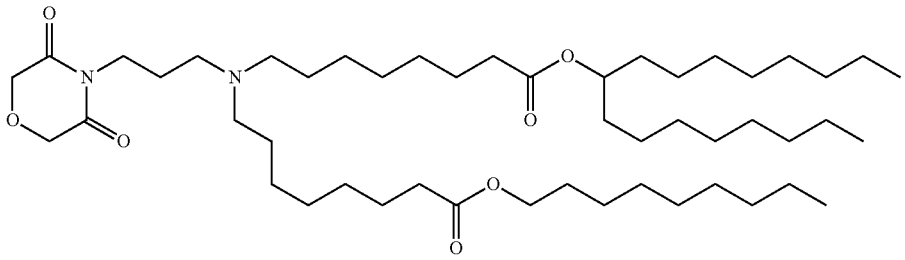

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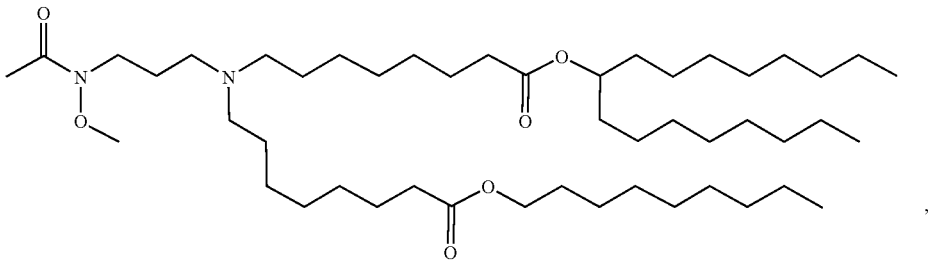

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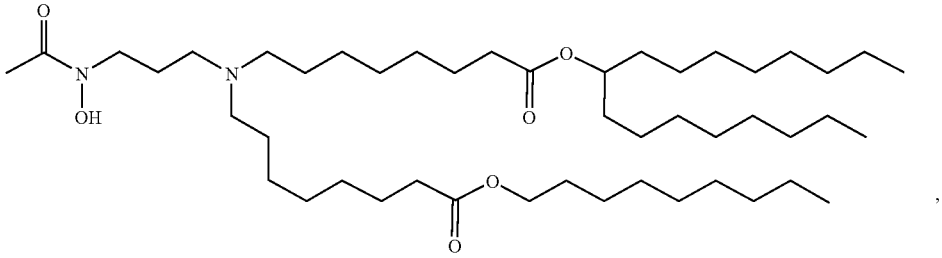

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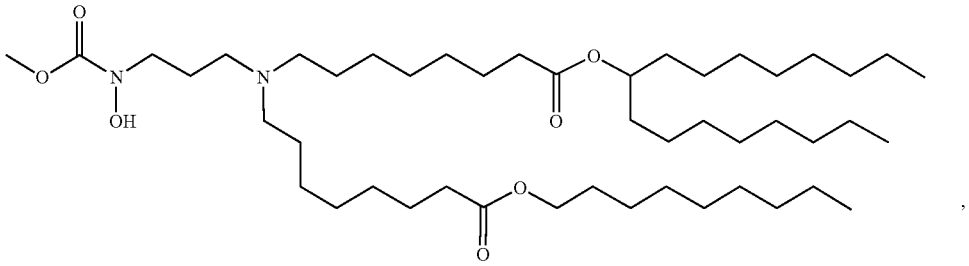

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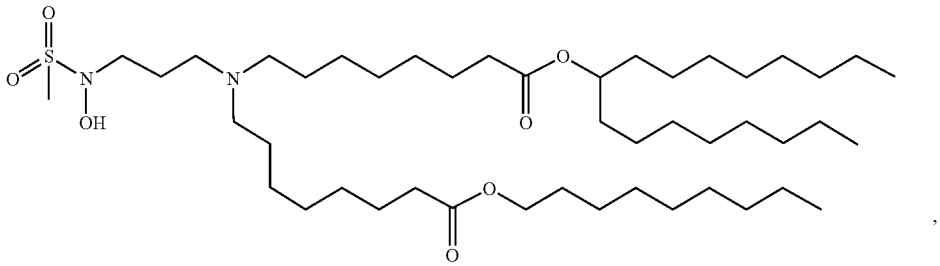

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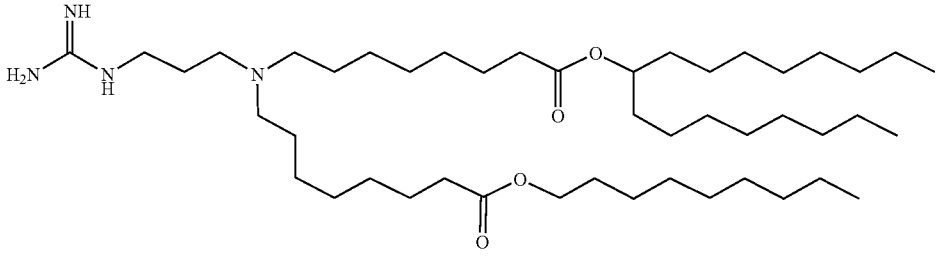

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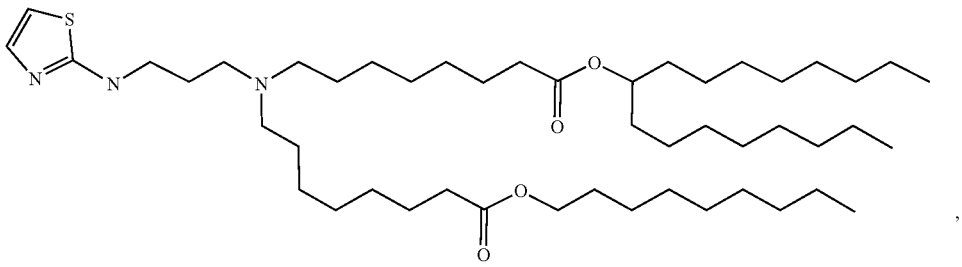

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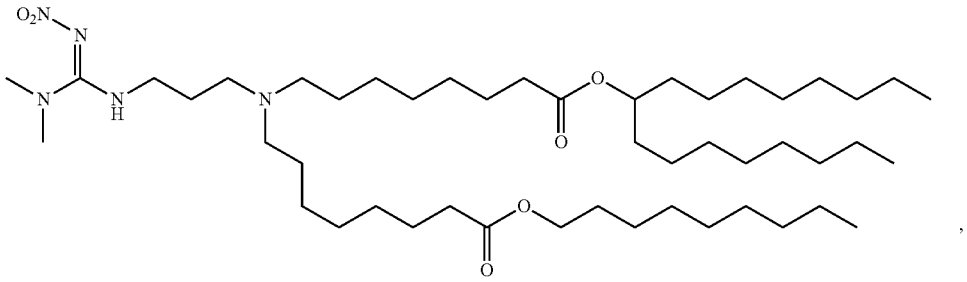

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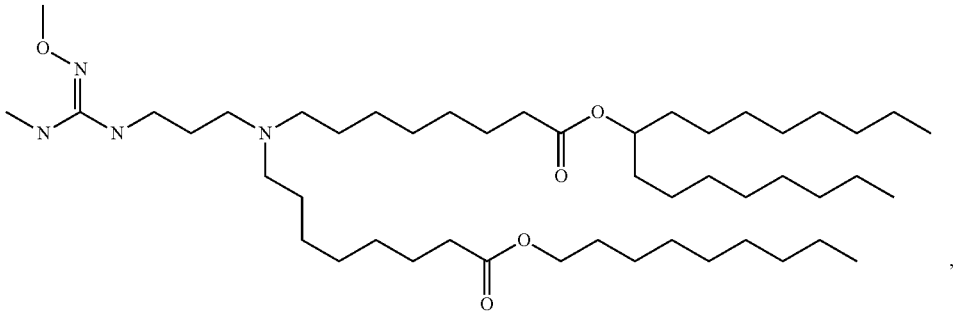

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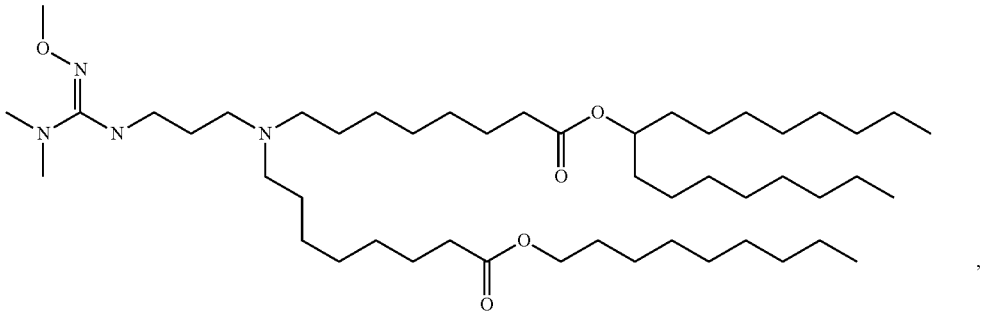
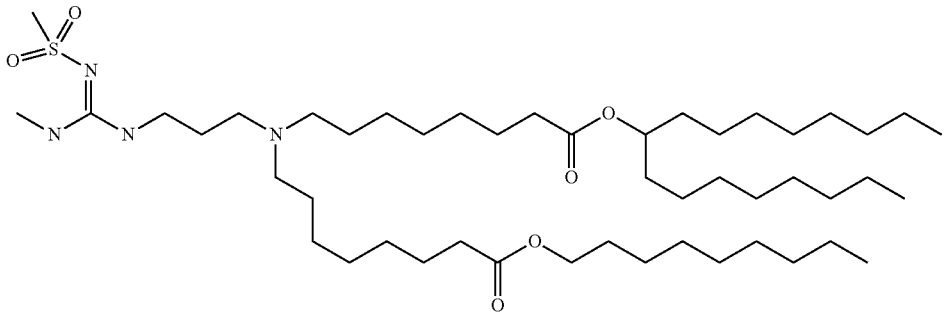
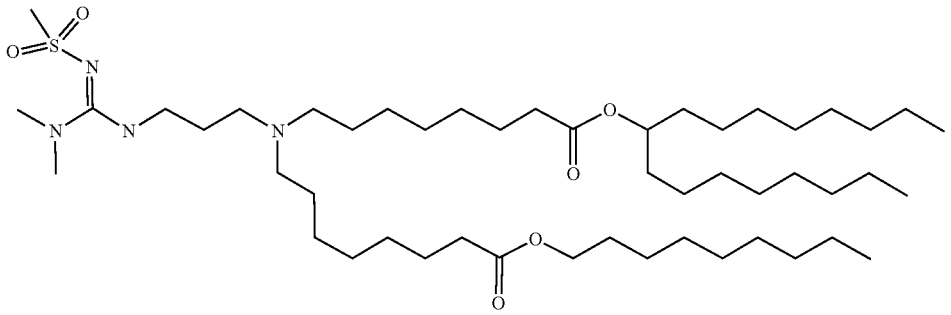


(Compound 212)



(Compound 213)



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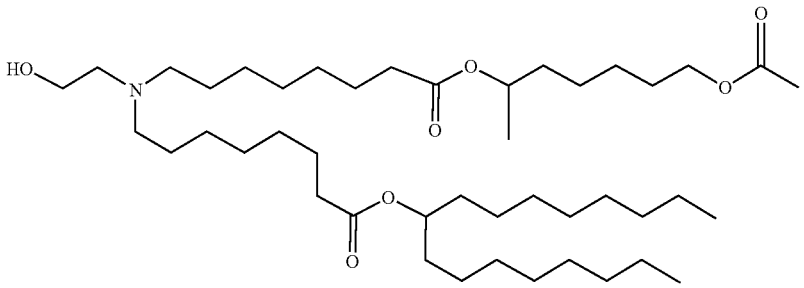
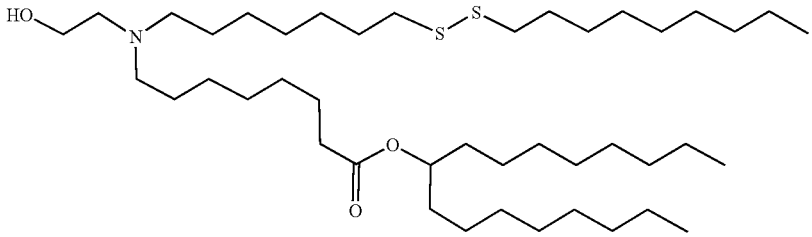
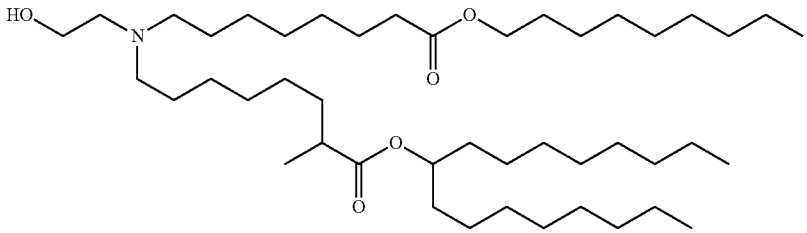
(Compound 214)



(Compound 215)



(Compound 216)



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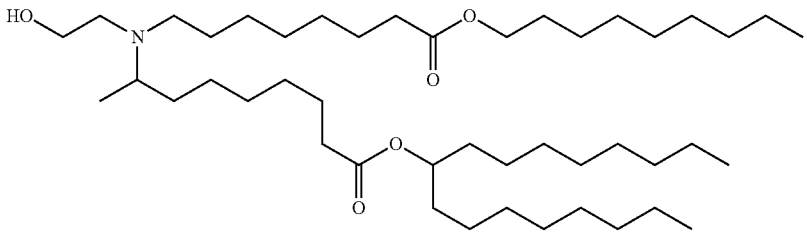

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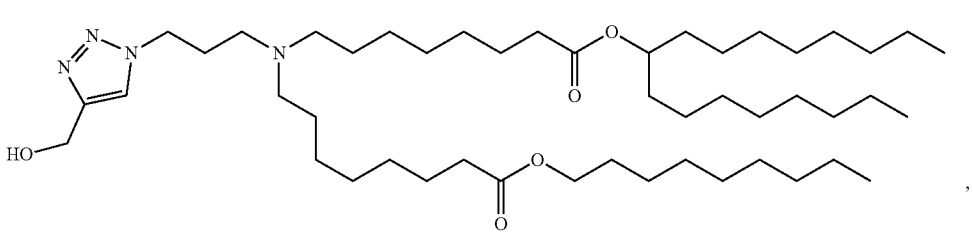

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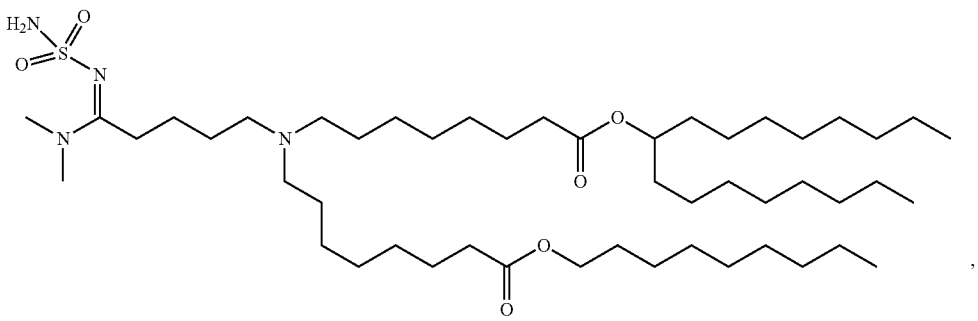

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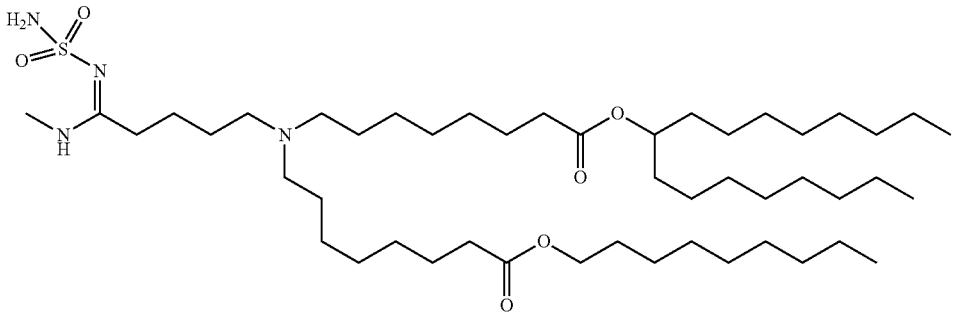

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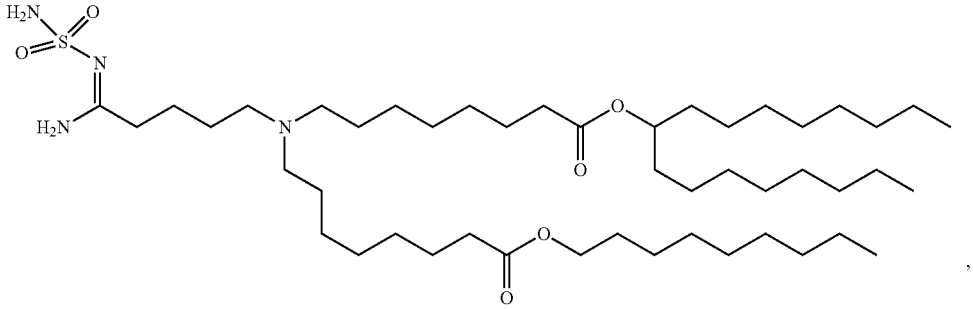

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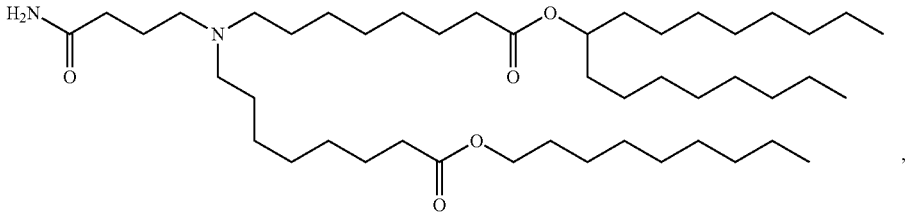

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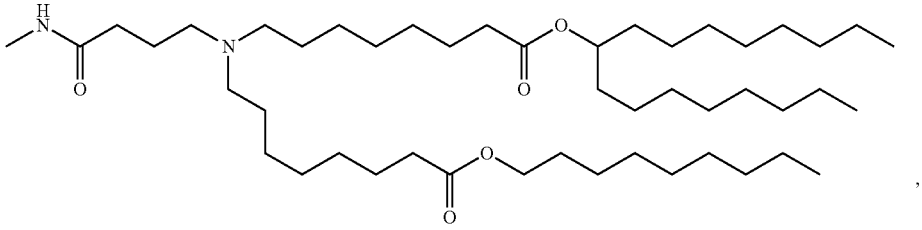

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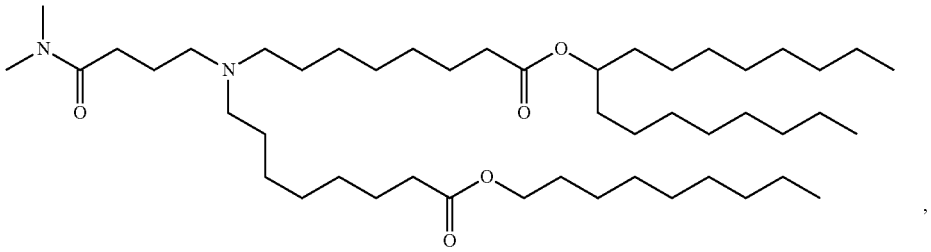

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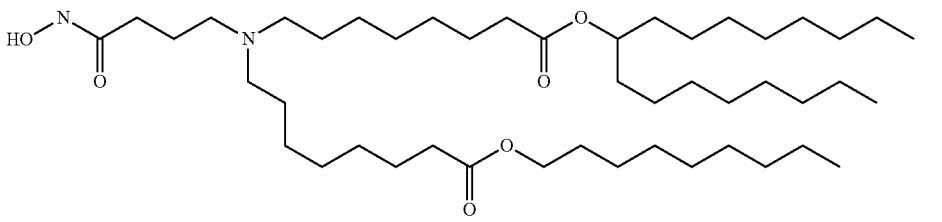

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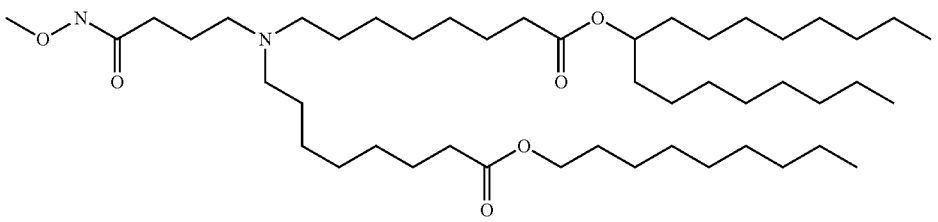
(Compound 226)



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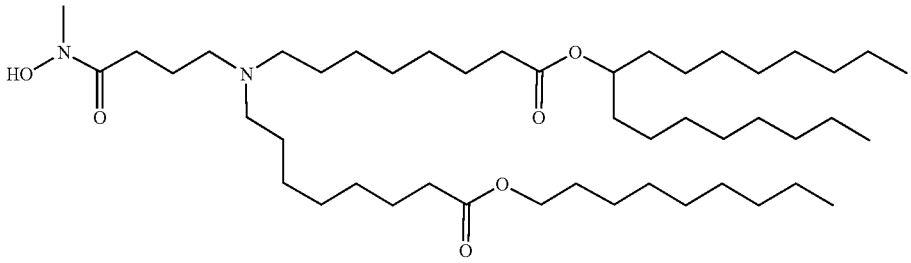

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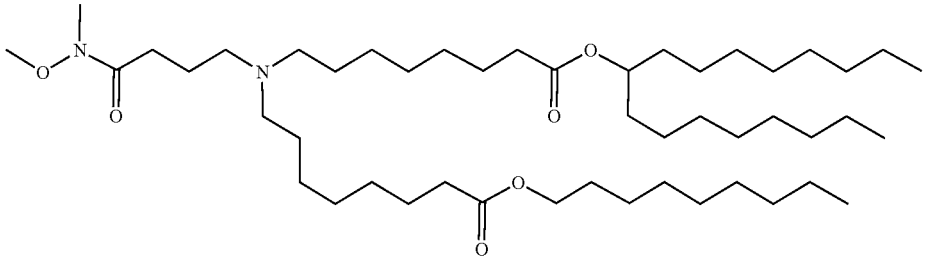
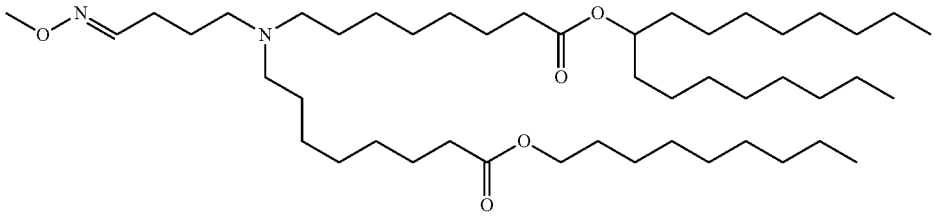
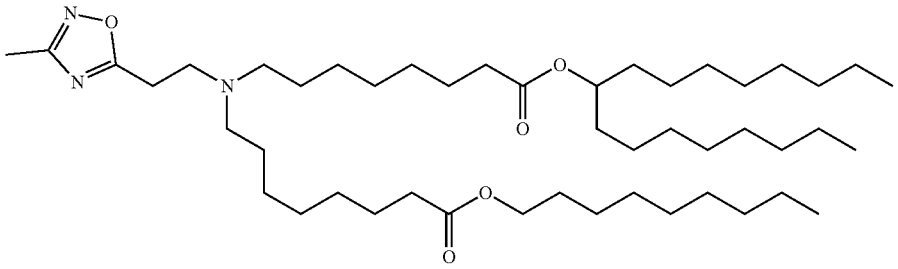


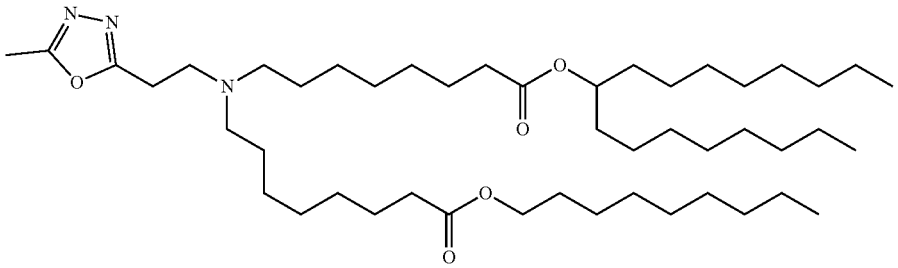
(Compound 229)



(Compound 230)



(Compound 231)



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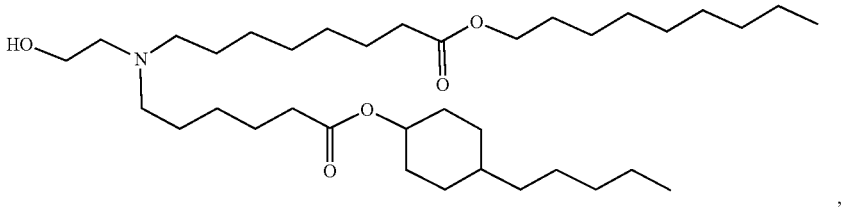
(Compound 232)

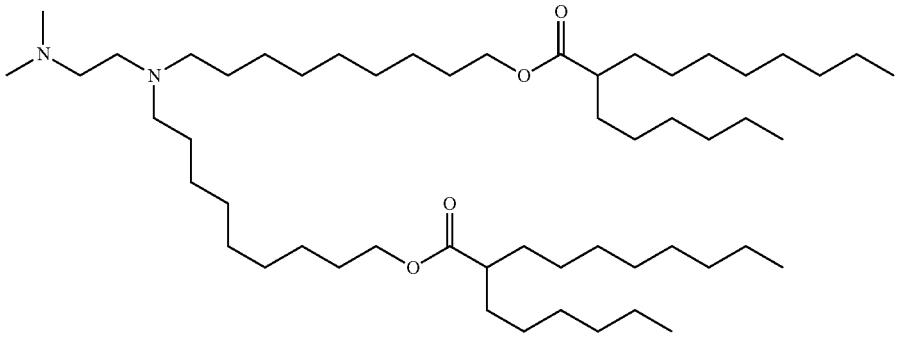


,

and salts and isomers thereof.

In some embodiments, a nanoparticle comprises the following compound:

(Compound 233)



or salts and isomers thereof.

In some embodiments, the disclosure features a nanoparticle composition including a lipid component comprising a compound as described herein (e.g., a compound according to Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe)).

In some embodiments, the disclosure features a pharmaceutical composition comprising a nanoparticle composition according to the preceding embodiments and a pharmaceutically acceptable carrier. For example, the pharmaceutical composition is refrigerated or frozen for storage and/or shipment (e.g., being stored at a temperature of 4° C. or lower, such as a temperature between about −150° C. and about 0° C. or between about −80° C. and about −20° C. (e.g., about −5° C., −10° C., −15° C., −20° C., −25° C., −30° C., −40° C., −50° C., −60° C., −70° C., −80° C., −90° C., −130° C. or −150° C.). For example, the pharmaceutical composition is a solution that is refrigerated for storage and/or shipment at, for example, about −20° C., −30° C., −40° C., −50° C., −60° C., −70° C., or −80° C.

In some embodiments, the disclosure provides a method of delivering a therapeutic and/or prophylactic (e.g., RNA, such as mRNA) to a cell (e.g., a mammalian cell). This method includes the step of administering to a subject (e.g., a mammal, such as a human) a nanoparticle composition including (i) a lipid component including a phospholipid (such as a polyunsaturated lipid), a PEG lipid, a structural lipid, and a compound of Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe) and (ii) a therapeutic and/or prophylactic, in which administering involves contacting the cell with the nanoparticle composition, whereby the therapeutic and/or prophylactic is delivered to the cell.

In some embodiments, the disclosure provides a method of producing a polypeptide of interest in a cell (e.g., a mammalian cell). The method includes the step of contacting the cell with a nanoparticle composition including (i) a lipid component including a phospholipid (such as a polyunsaturated lipid), a PEG lipid, a structural lipid, and a compound of Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe) and (ii) an mRNA encoding the polypeptide of interest, whereby the mRNA is capable of being translated in the cell to produce the polypeptide.

In some embodiments, the disclosure provides a method of treating a disease or disorder in a mammal (e.g., a human) in need thereof. The method includes the step of administering to the mammal a therapeutically effective amount of a nanoparticle composition including (i) a lipid component including a phospholipid (such as a polyunsaturated lipid), a PEG lipid, a structural lipid, and a compound of Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe) and (ii) a therapeutic and/or prophylactic (e.g., an mRNA).

In some embodiments, the disease or disorder is characterized by dysfunctional or aberrant protein or polypeptide activity. For example, the disease or disorder is selected from the group consisting of rare diseases, infectious diseases, cancer and proliferative diseases, genetic diseases (e.g., cystic fibrosis), autoimmune diseases, diabetes, neurodegenerative diseases, cardio- and reno-vascular diseases, and metabolic diseases.

In some embodiments, the disclosure provides a method of delivering (e.g., specifically delivering) a therapeutic and/or prophylactic to a mammalian organ (e.g., a liver, spleen, lung, or femur). This method includes the step of administering to a subject (e.g., a mammal) a nanoparticle composition including (i) a lipid component including a phospholipid, a PEG lipid, a structural lipid, and a compound of Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe) and (ii) a therapeutic and/or prophylactic (e.g., an mRNA), in which administering involves contacting the cell with the nanoparticle composition, whereby the therapeutic and/or prophylactic is delivered to the target organ (e.g., a liver, spleen, lung, or femur).

In some embodiments, the disclosure features a method for the enhanced delivery of a therapeutic and/or prophylactic (e.g., an mRNA) to a target tissue (e.g., a liver, spleen, lung, or femur). This method includes administering to a subject (e.g., a mammal) a nanoparticle composition, the composition including (i) a lipid component including a compound of Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe), a phospholipid, a structural lipid, and a PEG lipid; and (ii) a therapeutic and/or prophylactic, the administering including contacting the target tissue with the nanoparticle composition, whereby the therapeutic and/or prophylactic is delivered to the target tissue.

In some embodiments, the disclosure features a method of lowering immunogenicity comprising introducing the nanoparticle composition of the disclosure into cells, wherein the nanoparticle composition reduces the induction of the cellular immune response of the cells to the nanoparticle composition, as compared to the induction of the cellular immune response in cells induced by a reference composition which comprises a reference lipid instead of a compound of Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe). For example, the cellular immune response is an innate immune response, an adaptive immune response, or both.

The disclosure also includes methods of synthesizing a compound of Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe) and methods of making a nanoparticle composition including a lipid component comprising the compound of Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe).

Modes of Vaccine Administration

Respiratory virus RNA (e.g. mRNA) vaccines may be administered by any route which results in a therapeutically effective outcome. These include, but are not limited, to intradermal, intramuscular, and/or subcutaneous administration. The present disclosure provides methods comprising administering RNA (e.g., mRNA) vaccines to a subject in need thereof. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the disease, the particular composition, its mode of administration, its mode of activity, and the like. Respiratory virus RNA (e.g., mRNA) vaccines compositions are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of RNA (e.g., mRNA) vaccine compositions may be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective, prophylactically effective, or appropriate imaging dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

In some embodiments, respiratory virus RNA (e.g. mRNA) vaccines compositions may be administered at dosage levels sufficient to deliver 0.0001 mg/kg to 100 mg/kg, 0.001 mg/kg to 0.05 mg/kg, 0.005 mg/kg to 0.05 mg/kg, 0.001 mg/kg to 0.005 mg/kg, 0.05 mg/kg to 0.5 mg/kg, 0.01 mg/kg to 50 mg/kg, 0.1 mg/kg to 40 mg/kg, 0.5 mg/kg to 30 mg/kg, 0.01 mg/kg to 10 mg/kg, 0.1 mg/kg to 10 mg/kg, or 1 mg/kg to 25 mg/kg, of subject body weight per day, one or more times a day, per week, per month, etc. to obtain the desired therapeutic, diagnostic, prophylactic, or imaging effect (see, e.g., the range of unit doses described in International Publication No WO2013078199, the contents of which are herein incorporated by reference in their entirety). The desired dosage may be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, every four weeks, every 2 months, every three months, every 6 months, etc. In some embodiments, the desired dosage may be delivered using multiple administrations (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations). When multiple administrations are employed, split dosing regimens such as those described herein may be used. In exemplary embodiments, respiratory virus RNA (e.g., mRNA) vaccines compositions may be administered at dosage levels sufficient to deliver 0.0005 mg/kg to 0.01 mg/kg, e.g., about 0.0005 mg/kg to about 0.0075 mg/kg, e.g., about 0.0005 mg/kg, about 0.001 mg/kg, about 0.002 mg/kg, about 0.003 mg/kg, about 0.004 mg/kg or about 0.005 mg/kg.

In some embodiments, respiratory virus RNA (e.g., mRNA) vaccine compositions may be administered once or twice (or more) at dosage levels sufficient to deliver 0.025 mg/kg to 0.250 mg/kg, 0.025 mg/kg to 0.500 mg/kg, 0.025 mg/kg to 0.750 mg/kg, or 0.025 mg/kg to 1.0 mg/kg.

In some embodiments, respiratory virus RNA (e.g., mRNA) vaccine compositions may be administered twice (e.g., Day 0 and Day 7, Day 0 and Day 14, Day 0 and Day 21, Day 0 and Day 28, Day 0 and Day 60, Day 0 and Day 90, Day 0 and Day 120, Day 0 and Day 150, Day 0 and Day 180, Day 0 and 3 months later, Day 0 and 6 months later, Day 0 and 9 months later, Day 0 and 12 months later, Day 0 and 18 months later, Day 0 and 2 years later, Day 0 and 5 years later, or Day 0 and 10 years later) at a total dose of or at dosage levels sufficient to deliver a total dose of 0.0100 mg, 0.025 mg, 0.050 mg, 0.075 mg, 0.100 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.200 mg, 0.225 mg, 0.250 mg, 0.275 mg, 0.300 mg, 0.325 mg, 0.350 mg, 0.375 mg, 0.400 mg, 0.425 mg, 0.450 mg, 0.475 mg, 0.500 mg, 0.525 mg, 0.550 mg, 0.575 mg, 0.600 mg, 0.625 mg, 0.650 mg, 0.675 mg, 0.700 mg, 0.725 mg, 0.750 mg, 0.775 mg, 0.800 mg, 0.825 mg, 0.850 mg, 0.875 mg, 0.900 mg, 0.925 mg, 0.950 mg, 0.975 mg, or 1.0 mg. Higher and lower dosages and frequency of administration are encompassed by the present disclosure. For example, a respiratory virus RNA (e.g., mRNA) vaccine composition may be administered three or four times.

In some embodiments, respiratory virus RNA (e.g., mRNA) vaccine compositions may be administered twice (e.g., Day 0 and Day 7, Day 0 and Day 14, Day 0 and Day 21, Day 0 and Day 28, Day 0 and Day 60, Day 0 and Day 90, Day 0 and Day 120, Day 0 and Day 150, Day 0 and Day 180, Day 0 and 3 months later, Day 0 and 6 months later, Day 0 and 9 months later, Day 0 and 12 months later, Day 0 and 18 months later, Day 0 and 2 years later, Day 0 and 5 years later, or Day 0 and 10 years later) at a total dose of or at dosage levels sufficient to deliver a total dose of 0.010 mg, 0.025 mg, 0.100 mg or 0.400 mg.

In some embodiments, the respiratory virus RNA (e.g., mRNA) vaccine for use in a method of vaccinating a subject is administered to the subject as a single dosage of between 10 μg/kg and 400 μg/kg of the nucleic acid vaccine (in an effective amount to vaccinate the subject). In some embodiments the RNA (e.g., mRNA) vaccine for use in a method of vaccinating a subject is administered to the subject as a single dosage of between 10 μg and 400 μg of the nucleic acid vaccine (in an effective amount to vaccinate the subject). In some embodiments, a respiratory virus RNA (e.g.,

mRNA) vaccine for use in a method of vaccinating a subject is administered to the subject as a single dosage of 25-1000 μg (e.g., a single dosage of mRNA encoding hMPV, PIV3, RSV, MeV and/or BetaCoV antigen). In some embodiments, a respiratory virus RNA (e.g., mRNA) vaccine is administered to the subject as a single dosage of 25, 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950 or 1000 μg. For example, a respiratory virus RNA (e.g., mRNA) vaccine may be administered to a subject as a single dose of 25-100, 25-500, 50-100, 50-500, 50-1000, 100-500, 100-1000, 250-500, 250-1000, or 500-1000 μg. In some embodiments, a respiratory virus RNA (e.g., mRNA) vaccine for use in a method of vaccinating a subject is administered to the subject as two dosages, the combination of which equals 25-1000 μg of the respiratory virus RNA (e.g., mRNA) vaccine.

A respiratory virus RNA (e.g. mRNA) vaccine pharmaceutical composition described herein can be formulated into a dosage form described herein, such as an intranasal, intratracheal, or injectable (e.g., intravenous, intraocular, intravitreal, intramuscular, intradermal, intracardiac, intraperitoneal, and subcutaneous).

Respiratory Virus RNA (e.g., mRNA) Vaccine Formulations and Methods of Use

Some aspects of the present disclosure provide formulations of the respiratory virus RNA (e.g., mRNA) vaccine, wherein the RNA (e.g., mRNA) vaccine is formulated in an effective amount to produce an antigen specific immune response in a subject (e.g., production of antibodies specific to an hMPV, PIV3, RSV, MeV and/or BetaCoV antigenic polypeptide). "An effective amount" is a dose of an RNA (e.g., mRNA) vaccine effective to produce an antigen-specific immune response. Also provided herein are methods of inducing an antigen-specific immune response in a subject.

In some embodiments, the antigen-specific immune response is characterized by measuring an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide antibody titer produced in a subject administered a respiratory virus RNA (e.g., mRNA) vaccine as provided herein. An antibody titer is a measurement of the amount of antibodies within a subject, for example, antibodies that are specific to a particular antigen (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) or epitope of an antigen. Antibody titer is typically expressed as the inverse of the greatest dilution that provides a positive result. Enzyme-linked immunosorbent assay (ELISA) is a common assay for determining antibody titers, for example.

In some embodiments, an antibody titer is used to assess whether a subject has had an infection or to determine whether immunizations are required. In some embodiments, an antibody titer is used to determine the strength of an autoimmune response, to determine whether a booster immunization is needed, to determine whether a previous vaccine was effective, and to identify any recent or prior infections. In accordance with the present disclosure, an antibody titer may be used to determine the strength of an immune response induced in a subject by the respiratory virus RNA (e.g., mRNA) vaccine.

In some embodiments, an anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a subject is increased by at least 1 log relative to a control. For example, anti-antigenic polypeptide antibody titer produced in a subject may be increased by at least 1.5, at least 2, at least 2.5, or at least 3 log relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased by 1, 1.5, 2, 2.5 or 3 log relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased by 1-3 log relative to a control. For example, the anti-antigenic polypeptide antibody titer produced in a subject may be increased by 1-1.5, 1-2, 1-2.5, 1-3, 1.5-2, 1.5-2.5, 1.5-3, 2-2.5, 2-3, or 2.5-3 log relative to a control.

In some embodiments, the anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a subject is increased at least 2 times relative to a control. For example, the anti-antigenic polypeptide antibody titer produced in a subject may be increased at least 3 times, at least 4 times, at least 5 times, at least 6 times, at least 7 times, at least 8 times, at least 9 times, or at least 10 times relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased 2, 3, 4, 5, 6, 7, 8, 9, or 10 times relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in a subject is increased 2-10 times relative to a control. For example, the anti-antigenic polypeptide antibody titer produced in a subject may be increased 2-10, 2-9, 2-8, 2-7, 2-6, 2-5, 2-4, 2-3, 3-10, 3-9, 3-8, 3-7, 3-6, 3-5, 3-4, 4-10, 4-9, 4-8, 4-7, 4-6, 4-5, 5-10, 5-9, 5-8, 5-7, 5-6, 6-10, 6-9, 6-8, 6-7, 7-10, 7-9, 7-8, 8-10, 8-9, or 9-10 times relative to a control.

A control, in some embodiments, is the anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a subject who has not been administered a respiratory virus RNA (e.g., mRNA) vaccine of the present disclosure. In some embodiments, a control is an anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a subject who has been administered a live attenuated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine. An attenuated vaccine is a vaccine produced by reducing the virulence of a viable (live). An attenuated virus is altered in a manner that renders it harmless or less virulent relative to live, unmodified virus. In some embodiments, a control is an anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a subject administered inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine. In some embodiments, a control is an anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a subject administered a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine. Recombinant protein vaccines typically include protein antigens that either have been produced in a heterologous expression system (e.g., bacteria or yeast) or purified from large amounts of the pathogenic organism. In some embodiments, a control is an anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a subject who has been administered an hMPV, PIV3, RSV, MeV and/or BetaCoV virus-like particle (VLP) vaccine. For example, an hMPV VLP vaccine used as a control may be a hMPV VLPs, comprising (or consisting of) viral matrix (M) and fusion (F) proteins, generated by expressing viral proteins in suspension-adapted human embryonic kidney epithelial (293-F) cells (see, e.g., Cox R G et al., *J Virol.* 2014 June; 88(11): 6368-6379, the contents of which are herein incorporated by reference).

In some embodiments, an effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a dose that is reduced compared to the standard of care dose of a recombinant hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine. A "standard of care," as provided herein, refers to a medical or psychological treatment guideline and can be general or specific. "Standard of care" specifies appropriate treatment based on scientific evidence and collaboration between medical professionals involved in the treatment of a given condition. It is the diagnostic and treatment process that a physician/clinician should follow for a certain type of patient, illness or clinical circumstance. A "standard of care dose," as provided herein, refers to the dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine, or a live attenuated or inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine, that a physician/clinician or other medical professional would administer to a subject to treat or prevent hMPV, PIV3, RSV, MeV and/or BetaCoV, or a hMPV-, PIV3-, RSV-, MeV- and/or BetaCoV-related condition, while following the standard of care guideline for treating or preventing hMPV, PIV3, RSV, MeV and/or BetaCoV, or a hMPV-, PIV3-, RSV-, MeV- and/or BetaCoV-related condition.

In some embodiments, the anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a subject administered an effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is equivalent to an anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a control subject administered a standard of care dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine or a live attenuated or inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine.

In some embodiments, an effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a dose equivalent to an at least 2-fold reduction in a standard of care dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine. For example, an effective amount of a respiratory virus RNA (e.g., mRNA) vaccine may be a dose equivalent to an at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, or at least 10-fold reduction in a standard of care dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine. In some embodiments, an effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a dose equivalent to an at least at least 100-fold, at least 500-fold, or at least 1000-fold reduction in a standard of care dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine. In some embodiments, an effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a dose equivalent to a 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 20-, 50-, 100-, 250-, 500-, or 1000-fold reduction in a standard of care dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine. In some embodiments, the anti-antigenic polypeptide antibody titer produced in a subject administered an effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant or protein hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine or a live attenuated or inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine. In some embodiments, an effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a dose equivalent to a 2-fold to 1000-fold (e.g., 2-fold to 100-fold, 10-fold to 1000-fold) reduction in the standard of care dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine, wherein the anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine or a live attenuated or inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine.

In some embodiments, the effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a dose equivalent to a 2 to 1000-, 2 to 900-, 2 to 800-, 2 to 700-, 2 to 600-, 2 to 500-, 2 to 400-, 2 to 300-, 2 to 200-, 2 to 100-, 2 to 90-, 2 to 80-, 2 to 70-, 2 to 60-, 2 to 50-, 2 to 40-, 2 to 30-, 2 to 20-, 2 to 10-, 2 to 9-, 2 to 8-, 2 to 7-, 2 to 6-, 2 to 5-, 2 to 4-, 2 to 3-, 3 to 1000-, 3 to 900-, 3 to 800-, 3 to 700-, 3 to 600-, 3 to 500-, 3 to 400-, 3 to 3 to 00-, 3 to 200-, 3 to 100-, 3 to 90-, 3 to 80-, 3 to 70-, 3 to 60-, 3 to 50-, 3 to 40-, 3 to 30-, 3 to 20-, 3 to 10-, 3 to 9-, 3 to 8-, 3 to 7-, 3 to 6-, 3 to 5-, 3 to 4-, 4 to 1000-, 4 to 900-, 4 to 800-, 4 to 700-, 4 to 600- , 4 to 500-, 4 to 400-, 4 to 4 to 00-, 4 to 200-, 4 to 100-, 4 to 90-, 4 to 80-, 4 to 70-, 4 to 60-, 4 to 50-, 4 to 40-, 4 to 30-, 4 to 20-, 4 to 10-, 4 to 9-, 4 to 8-, 4 to 7-, 4 to 6-, 4 to 5-, 4 to 4-, 5 to 1000-, 5 to 900-, 5 to 800-, 5 to 700-, 5 to 600-, 5 to 500-, 5 to 400-, 5 to 300-, 5 to 200-, 5 to 100-, 5 to 90-, 5 to 80-, 5 to 70-, 5 to 60-, 5 to 50-, 5 to 40-, 5 to 30-, 5 to 20-, 5 to 10-, 5 to 9-, 5 to 8-, 5 to 7-, 5 to 6-, 6 to 1000-, 6 to 900-, 6 to 800-, 6 to 700-, 6 to 600-, 6 to 500-, 6 to 400-, 6 to 300-, 6 to 200-, 6 to 100-, 6 to 90-, 6 to 80-, 6 to 70-, 6 to 60-, 6 to 50-, 6 to 40-, 6 to 30-, 6 to 20-, 6 to 10-, 6 to 9-, 6 to 8-, 6 to 7-, 7 to 1000-, 7 to 900-, 7 to 800-, 7 to 700-, 7 to 600-, 7 to 500-, 7 to 400-, 7 to 300-, 7 to 200-, 7 to 100-, 7 to 90-, 7 to 80-, 7 to 70-, 7 to 60-, 7 to 50-, 7 to 40-, 7 to 30-, 7 to 20-, 7 to 10-, 7 to 9-, 7 to 8-, 8 to 1000-, 8 to 900-, 8 to 800-, 8 to 700-, 8 to 600-, 8 to 500-, 8 to 400-, 8 to 300-, 8 to 200-, 8 to 100-, 8 to 90-, 8 to 80-, 8 to 70-, 8 to 60-, 8 to 50-, 8 to 40-, 8 to 30-, 8 to 20-, 8 to 10-, 8 to 9-, 9 to 1000-, 9 to 900-, 9 to 800-, 9 to 700-, 9 to 600-, 9 to 500-, 9 to 400-, 9 to 300-, 9 to 200-, 9 to 100-, 9 to 90-, 9 to 80-, 9 to 70-, 9 to 60-, 9 to 50-, 9 to 40-, 9 to 30-, 9 to 20-, 9 to 10-, 10 to 1000-, 10 to 900-, 10 to 800-, 10 to 700-, 10 to 600-, 10 to 500-, 10 to 400-, 10 to 300-, 10 to 200-, 10 to 100-, 10 to 90-, 10 to 80-, 10 to 70-, 10 to 60-, 10 to 50-, 10 to 40-, 10 to 30-, 10 to 20-, 20 to 1000-, 20 to 900-, 20 to 800-, 20 to 700-, 20 to 600-, 20 to 500-, 20 to 400-, 20 to 300-, 20 to 200-, 20 to 100-, 20 to 90-, 20 to 80-, 20 to 70-, 20 to 60-, 20 to 50-, 20 to 40-, 20 to 30-, 30 to 1000-, 30 to 900-, 30 to 800-, 30 to 700-, 30 to 600-, 30 to 500-, 30 to 400-, 30 to 300-, 30 to 200-, 30 to 100-, 30 to 90-, 30 to 80-, 30 to 70-, 30 to 60-, 30 to 50-, 30 to 40-, 40 to 1000-, 40 to 900-, 40 to 800-, 40 to 700-, 40 to 600-, 40 to 500-, 40 to 400-, 40 to 300-, 40 to 200-, 40 to 100-, 40 to 90-, 40 to 80-, 40 to 70-, 40 to 60-, 40 to 50-, 50 to 1000-, 50 to 900-, 50 to 800-, 50 to 700-, 50 to 600-, 50 to 500-, 50 to 400-, 50 to 300-, 50 to 200-, 50 to 100-, 50 to 90-, 50 to 80-, 50 to 70-, 50 to 60-, 60 to 1000-, 60 to 900-, 60 to 800-, 60 to 700-, 60 to 600-, 60 to 500-, 60 to 400-, 60 to 300-, 60 to 200-, 60 to 100-, 60 to 90-, 60 to 80-, 60 to 70-, 70 to 1000-, 70 to 900-, 70 to 800-, 70 to 700-, 70 to 600-, 70 to 500-, 70 to 400-, 70 to 300-, 70 to 200-, 70 to 100-, 70 to 90-, 70 to 80-, 80 to 1000-, 80 to 900-, 80 to 800-, 80 to 700-, 80 to 600-, 80 to 500-, 80 to 400-, 80 to 300-, 80 to 200-, 80 to 100-, 80 to 90-, 90 to 1000-, 90 to 900-, 90 to 800-, 90 to 700-, 90 to 600-, 90 to 500-, 90 to 400-, 90 to 300-, 90 to 200-, 90 to 100-, 100 to 1000-, 100 to 900-, 100 to 800-, 100 to 700-, 100 to 600-, 100 to 500-, 100 to 400-, 100 to 300-, 100 to 200-, 200 to

1000-, 200 to 900-, 200 to 800-, 200 to 700-, 200 to 600-, 200 to 500-, 200 to 400-, 200 to 300-, 300 to 1000-, 300 to 900-, 300 to 800-, 300 to 700-, 300 to 600-, 300 to 500-, 300 to 400-, 400 to 1000-, 400 to 900-, 400 to 800-, 400 to 700-, 400 to 600-, 400 to 500-, 500 to 1000-, 500 to 900-, 500 to 800-, 500 to 700-, 500 to 600-, 600 to 1000-, 600 to 900-, 600 to 800-, 600 to 700-, 700 to 1000-, 700 to 900-, 700 to 800-, 800 to 1000-, 800 to 900-, or 900 to 1000-fold reduction in the standard of care dose of a recombinant hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine or a live attenuated or inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine. In some embodiments, the effective amount is a dose equivalent to (or equivalent to an at least) 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 20-, 30-, 40-, 50-, 60-, 70-, 80-, 90-, 100-, 110-, 120-, 130-, 140-, 150-, 160-, 170-, 1280-, 190-, 200-, 210-, 220-, 230-, 240-, 250-, 260-, 270-, 280-, 290-, 300-, 310-, 320-, 330-, 340-, 350-, 360-, 370-, 380-, 390-, 400-, 410-, 420-, 430-, 440-, 450-, 4360-, 470-, 480-, 490-, 500-, 510-, 520-, 530-, 540-, 550-, 560-, 5760-, 580-, 590-, 600-, 610-, 620-, 630-, 640-, 650-, 660-, 670-, 680-, 690-, 700-, 710-, 720-, 730-, 740-, 750-, 760-, 770-, 780-, 790-, 800-, 810-, 820-, 830-, 840-, 850-, 860-, 870-, 880-, 890-, 900-, 910-, 920-, 930-, 940-, 950-, 960-, 970-, 980-, 990-, or 1000-fold reduction in the standard of care dose of a recombinant hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine. In some embodiments, an anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine or a live attenuated or inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine.

In some embodiments, the effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a total dose of 50-1000 μg. In some embodiments, the effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a total dose of 50-1000, 50-900, 50-800, 50-700, 50-600, 50-500, 50-400, 50-300, 50-200, 50-100, 50-90, 50-80, 50-70, 50-60, 60-1000, 60-900, 60-800, 60-700, 60-600, 60-500, 60-400, 60-300, 60-200, 60-100, 60-90, 60-80, 60-70, 70-1000, 70-900, 70-800, 70-700, 70-600, 70-500, 70-400, 70-300, 70-200, 70-100, 70-90, 70-80, 80-1000, 80-900, 80-800, 80-700, 80-600, 80-500, 80-400, 80-300, 80-200, 80-100, 80-90, 90-1000, 90-900, 90-800, 90-700, 90-600, 90-500, 90-400, 90-300, 90-200, 90-100, 100-1000, 100-900, 100-800, 100-700, 100-600, 100-500, 100-400, 100-300, 100-200, 200-1000, 200-900, 200-800, 200-700, 200-600, 200-500, 200-400, 200-300, 300-1000, 300-900, 300-800, 300-700, 300-600, 300-500, 300-400, 400-1000, 400-900, 400-800, 400-700, 400-600, 400-500, 500-1000, 500-900, 500-800, 500-700, 500-600, 600-1000, 600-900, 600-900, 600-700, 700-1000, 700-900, 700-800, 800-1000, 800-900, or 900-1000 μg. In some embodiments, the effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a total dose of 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950 or 1000 μg. In some embodiments, the effective amount is a dose of 25-500 μg administered to the subject a total of two times. In some embodiments, the effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a dose of 25-500, 25-400, 25-300, 25-200, 25-100, 25-50, 50-500, 50-400, 50-300, 50-200, 50-100, 100-500, 100-400, 100-300, 100-200, 150-500, 150-400, 150-300, 150-200, 200-500, 200-400, 200-300, 250-500, 250-400, 250-300, 300-500, 300-400, 350-500, 350-400, 400-500 or 450-500 μg administered to the subject a total of two times. In some embodiments, the effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a total dose of 25, 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 μg administered to the subject a total of two times.

EXAMPLES OF ADDITIONAL EMBODIMENTS OF THE DISCLOSURE

Additional embodiments of the present disclosure are encompassed by the following numbered paragraphs:

1. A respiratory virus vaccine, comprising: at least one ribonucleic acid (RNA) polynucleotide having an open reading frame encoding at least one, at least two, at least three, at least four or at least five antigenic polypeptides selected from human metapneumovirus (hMPV) antigenic polypeptides or immunogenic fragments thereof, human parainfluenza virus type 3 (PIV3) antigenic polypeptides or immunogenic fragments thereof, respiratory syncytial virus (RSV) antigenic polypeptides or immunogenic fragments thereof, measles virus (MeV) antigenic polypeptides or immunogenic fragments thereof, and betacoronavirus (BetaCoV) antigenic polypeptides or immunogenic fragments thereof.

2. The respiratory virus vaccine of paragraph 1, comprising: at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof and a PIV3 antigenic polypeptide or an immunogenic fragment thereof; or at least two RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof.

3. The respiratory virus vaccine of paragraph 2, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, and/or wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13.

4. The respiratory virus vaccine of paragraph 1, comprising: at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof and a RSV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof.

5. The respiratory virus vaccine of paragraph 4, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8.

6. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immu-

nogenic fragment thereof and MeV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof.

7. The respiratory virus vaccine of paragraph 6, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, and/or wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50.

8. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

9. The respiratory virus vaccine of paragraph 8, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34.

10. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof and a RSV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof.

11. The respiratory virus vaccine of paragraph 10, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13.

12. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof and a MeV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof.

13. The respiratory virus vaccine of paragraph 12, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, and/or wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50.

14. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

15. The respiratory virus vaccine of paragraph 14, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34.

16. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof and a MeV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof.

17. The respiratory virus vaccine of paragraph 16, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50.

18. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

19. The respiratory virus vaccine of paragraph 18, wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34.

20. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a MeV antigenic polypeptide or an immu-

nogenic fragment thereof and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

21. The respiratory virus vaccine of paragraph 20, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34.

22. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a PIV3 antigenic polypeptide or an immunogenic fragment thereof, and a RSV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof.

23. The respiratory virus vaccine of paragraph 22, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, and/or wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13.

24. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a PIV3 antigenic polypeptide or an immunogenic fragment thereof, and a MeV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof.

25. The respiratory virus vaccine of paragraph 24, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, and/or wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50.

26. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a PIV3 antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

27. The respiratory virus vaccine of paragraph 26, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13 and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 23-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 23-34.

28. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, and a MeV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof.

29. The respiratory virus vaccine of paragraph 28, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, and/or wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50.

30. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, and one having an open

reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

31. The respiratory virus vaccine of paragraph 30, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 23-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 23-34.

32. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a MeV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

33. The respiratory virus vaccine of paragraph 32, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 23-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 23-34.

34. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, and a MeV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof.

35. The respiratory virus vaccine of paragraph 34, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, and/or wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50.

36. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

37. The respiratory virus vaccine of paragraph 36, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 23-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 23-34.

38. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, a MeV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

39. The respiratory virus vaccine of paragraph 38, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 23-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 23-34.

40. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, a MeV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

41. The respiratory virus vaccine of paragraph 40, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ

ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 23-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 23-34.

42. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a PIV3 antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, and a MeV antigenic polypeptide or an immunogenic fragment thereof; or

at least two, three or four RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof.

43. The respiratory virus vaccine of paragraph 42, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, and/or wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50.

44. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a PIV3 antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two, three or four RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

45. The respiratory virus vaccine of paragraph 44, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34.

46. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a PIV3 antigenic polypeptide or an immunogenic fragment thereof, a MeV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two, three or four RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

47. The respiratory virus vaccine of paragraph 46, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34.

48. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, a MeV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two, three or four RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

49. The respiratory virus vaccine of paragraph 48, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90%

or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34.

50. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, a MeV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two, three or four RNA polynucleotides, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

51. The respiratory virus vaccine of paragraph 50, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34.

52. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a PIV3 antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, a MeV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two, three, four or five RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

53. The respiratory virus vaccine of paragraph 52, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34.

54. The vaccine of any one of paragraphs 1-53, wherein at least one RNA polynucleotide has less than 80% identity to wild-type mRNA sequence.

55. The vaccine of any one of paragraphs 1-53, wherein at least one RNA polynucleotide has at least 80% identity to wild-type mRNA sequence, but does not include wild-type mRNA sequence.

56. The vaccine of any one of paragraphs 1-55, wherein at least one antigenic polypeptide has membrane fusion activity, attaches to cell receptors, causes fusion of viral and cellular membranes, and/or is responsible for binding of the virus to a cell being infected.

57. The vaccine of any one of paragraphs 1-56, wherein at least one RNA polynucleotide comprises at least one chemical modification.

58. The vaccine of paragraph 57, wherein the chemical modification is selected from pseudouridine, N1-methylpseudouridine, N1-ethylpseudouridine, 2-thiouridine, 4'-thiouridine, 5-methylcyto sine, 5-methyluridine, 2-thio-1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-pseudouridine, 2-thio-5-aza-uridine, 2-thio-dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-pseudouridine, 4-methoxy-2-thio-pseudouridine, 4-methoxy-pseudouridine, 4-thio-1-methyl-pseudouridine, 4-thio-pseudouridine, 5-aza-uridine, dihydropseudouridine, 5-methoxyuridine and 2'-O-methyl uridine.

59. The vaccine of paragraph 57 or 58, wherein the chemical modification is in the 5-position of the uracil.

60. The vaccine of any one of paragraphs 57-59, wherein the chemical modification is a N1-methylpseudouridine or N1-ethylpseudouridine.

61. The vaccine of any one of paragraphs 57-60, wherein at least 80%, at least 90% or 100% of the uracil in the open reading frame have a chemical modification.

62. The vaccine of any one of paragraphs 1-61, wherein at least one RNA polynucleotide further encodes at least one 5' terminal cap, optionally wherein the 5' terminal cap is 7mG(5')ppp(5')NlmpNp.

63. The vaccine of any one of paragraphs 1-62, wherein at least one antigenic polypeptide or immunogenic fragment thereof is fused to a signal peptide selected from: a HuIgGk signal peptide (METPAQLLFLLLLWLPDTTG; SEQ ID NO: 15); IgE heavy chain epsilon-1 signal peptide (MDWTWILFLVAAATRVHS; SEQ ID NO: 16); Japanese encephalitis PRM signal sequence (MLGSNSGQRVVFTILLLLVAPAYS; SEQ ID NO: 17), VSVg protein signal sequence (MKCLLYLAFLFIGVNCA; SEQ ID NO: 18) and Japanese encephalitis JEV signal sequence (MWLVSLAIVTACAGA; SEQ ID NO: 19).

64. The vaccine of paragraph 63, wherein the signal peptide is fused to the N-terminus or the C-terminus of at least one antigenic polypeptide.

65. The vaccine of any one of paragraphs 1-64, wherein the antigenic polypeptide or immunogenic fragment thereof comprises a mutated N-linked glycosylation site.

66. The vaccine of any one of paragraphs 1-65 formulated in a nanoparticle, optionally a a lipid nanoparticle.

67. The vaccine of paragraph 66, wherein the lipid nanoparticle comprises a cationic lipid, a PEG-modified lipid, a sterol and a non-cationic lipid; optionally wherein the lipid nanoparticle carrier comprises a molar ratio of about 20-60% cationic lipid, 0.5-15% PEG-modified lipid, 25-55% sterol, and 25% non-cationic lipid; optionally wherein the cationic lipid is an ionizable cationic lipid and the non-cationic lipid is a neutral lipid, and the sterol is a cholesterol; and optionally wherein the cationic lipid is selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319). Formula (II) 68. The vaccine of paragraph 66 or 67, wherein the nanoparticle (e.g., lipid nanoparticle) comprises a compound of Formula (I) and/or Formula (II), optionally Compound 3, 18, 20, 25, 26, 29, 30, 60, 108-112, or 122.

69. The vaccine of any one of paragraphs 1-68 further comprising an adjuvant, optionally a flagellin protein or peptide that optionally comprises an amino acid sequence identified by any one of SEQ ID NO: 54-56.

70. The vaccine of any one of paragraphs 1-69, wherein the open reading frame is codon-optimized.

71. The vaccine of any one of paragraphs 1-70 formulated in an effective amount to produce an antigen-specific immune response.

72. A method of inducing an immune response in a subject, the method comprising administering to the subject the vaccine of any one of paragraphs 1-71 in an amount effective to produce an antigen-specific immune response in the subject.

73. The method of paragraph 72, wherein the subject is administered a single dose of the vaccine, or wherein the subject is administered a first dose and then a booster dose of the vaccine.

74. The method of paragraph 72 or 73, wherein the vaccine is administered to the subject by intradermal injection or intramuscular injection.

75. The method of any one of paragraphs 72-74, wherein an anti-antigenic polypeptide antibody titer produced in the subject is increased by at least 1 log relative to a control, and/or wherein the anti-antigenic polypeptide antibody titer produced in the subject is increased at least 2 times relative to a control.

76. The method of any one of paragraphs 72-75, wherein the control is an anti-antigenic polypeptide antibody titer produced in a subject who has not been administered a vaccine against the virus, and/or wherein the control is an anti-antigenic polypeptide antibody titer produced in a subject who has been administered a live attenuated vaccine or an inactivated vaccine against the virus, and/or, wherein the control is an anti-antigenic polypeptide antibody titer produced in a subject who has been administered a recombinant protein vaccine or purified protein vaccine against the virus, and/or wherein the control is an anti-antigenic polypeptide antibody titer produced in a subject who has been administered a VLP vaccine against the virus.

77. The method of any one of paragraphs 72-76, wherein the effective amount is a dose equivalent to an at least 2-fold reduction in the standard of care dose of a recombinant protein vaccine or a purified protein vaccine against the virus, and wherein an anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant protein vaccine or a purified protein vaccine against the virus, respectively; and/or wherein the effective amount is a dose equivalent to an at least 2-fold reduction in the standard of care dose of a live attenuated vaccine or an inactivated vaccine against the virus, and wherein an anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a live attenuated vaccine or an inactivated vaccine against the virus, respectively; and/or wherein the effective amount is a dose equivalent to an at least 2-fold reduction in the standard of care dose of a VLP vaccine against the virus, and wherein an anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a VLP vaccine against the virus.

78. The method of any one of paragraphs 72-77, wherein the effective amount is a total dose of 50 μg-1000 μg, optionally wherein the effective amount is a dose of 25 μg, 100 μg, 400 μg, or 500 μg administered to the subject a total of two times.

79. The method of any one of paragraphs 72-78, wherein the efficacy of the vaccine against the virus is greater than 65%; and/or wherein the vaccine immunizes the subject against the virus for up to 2 years or wherein the vaccine immunizes the subject against the virus for more than 2 years.

80. The method of any one of paragraphs 72-79, wherein the subject has an age of about 5 years old or younger or wherein the subject has an age of about 60 years old or older; and/or wherein the subject has a chronic pulmonary disease; and/or the subject has been exposed to the virus, wherein the subject is infected with the virus, or wherein the subject is at risk of infection by the virus; and/or wherein the subject is immunocompromised.

81. The respiratory virus vaccine of any one of paragraphs 1-71, comprising at least one (e.g., at least two, at least three, at least four, or at least five) RNA polynucleotide having an open reading frame encoding at least one (e.g., at least two, at least three, at least four, or at least five) antigenic polypeptide selected from hMPV antigenic polypeptides (SEQ ID NO: 5-8), PIV3 antigenic polypeptides (SEQ ID NO: 12-13), RSV antigenic polypeptides, MeV antigenic polypeptides (SEQ ID NO: 47-50) and BetaCoV antigenic polypeptides (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1; (SEQ ID NO: 24-34)), formulated in a cationic lipid nanoparticle

(a) having a molar ratio of about 20-60% cationic lipid, about 5-25% non-cationic lipid, about 25-55% sterol, and about 0.5-15% PEG-modified lipid, and/or

(b) comprising a compound of Formula (I) and/or Formula (II),

wherein the at least one (e.g., at least two, at least three, at least four, or at least five) RNA polynucleotide comprises at least one chemical modification.

82. The respiratory virus vaccine of any one of paragraphs 1-71, comprising at least one (e.g., at least two, at least three, at least four, or at least five) RNA polynucleotide having an open reading frame encoding at least one (e.g., at least two, at least three, at least four, or at least five) antigenic polypeptide selected from hMPV antigenic polypeptides (SEQ ID NO: 5-8), PIV3 antigenic polypeptides (SEQ ID NO: 12-13), RSV antigenic polypeptides, MeV antigenic polypeptides (SEQ ID NO: 47-50) and BetaCoV antigenic polypeptides (e.g., MERS-CoV, SARS-CoV, HCoV-OC43,

HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1; (SEQ ID NO: 24-34)), formulated in a cationic lipid nanoparticle

(a) having a molar ratio of about 20-60% cationic lipid, about 5-25% non-cationic lipid, about 25-55% sterol, and about 0.5-15% PEG-modified lipid, and/or

(b) comprising at least one (e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14) Compound selected from Compounds 3, 18, 20, 25, 26, 29, 30, 60, 108-112 and 122.

83. The respiratory virus vaccine of paragraphs 81 or 82, wherein the at least one antigenic polypeptide is selected from hMPV antigentic polypeptides (e.g., SEQ ID NO: 5-8).

84. The respiratory virus vaccine of any one of paragraphs 81-83, wherein the at least one antigenic polypeptide is selected from PIV3 antigentic polypeptides (e.g., SEQ ID NO: 12-13).

85. The respiratory virus vaccine of any one of paragraphs 81-84, wherein the at least one antigenic polypeptide is selected from RSV antigentic polypeptides.

86. The respiratory virus vaccine of any one of paragraphs 81-85, wherein the at least one antigenic polypeptide is selected from MeV antigentic polypeptides (e.g., SEQ ID NO: 47-50).

87. The respiratory virus vaccine of any one of paragraphs 81-86, wherein the at least one antigenic polypeptide is selected from BetaCoV antigentic polypeptides (e.g., SEQ ID NO: 24-34).

88. The respiratory virus vaccine of paragraph 87, wherein the BetaCoV antigentic polypeptides are MERS antigentic polypeptides.

89. The respiratory virus vaccine of paragraph 87, wherein the BetaCoV antigentic polypeptides are SARS antigentic polypeptides.

90. The respiratory virus vaccine of any one of paragraphs 81-89, wherein the at least one (e.g., at least two, at least three, at least four, or at least five) RNA polynucleotide comprises at least one chemical modification (e.g., selected from pseudouridine, N1-methylpseudouridine, N1-ethylpseudouridine, 2-thiouridine, 4'-thiouridine, 5-methylcytosine, 5-methyluridine, 2-thio-1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-pseudouridine, 2-thio-5-aza-uridine, 2-thio-dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-pseudouridine, 4-methoxy-2-thio-pseudouridine, 4-methoxy-pseudouridine, 4-thio-1-methyl-pseudouridine, 4-thio-pseudouridine, 5-aza-uridine, dihydropseudouridine, 5-methoxyuridine and 2'-O-methyl uridine).

91. A respiratory virus vaccine, comprising:

at least one messenger ribonucleic acid (mRNA) polynucleotide having a 5' terminal cap, an open reading frame encoding at least one respiratory virus antigenic polypeptide, and a 3' polyA tail.

92. The vaccine of paragraph 91, wherein the at least one mRNA polynucleotide comprises a sequence identified by any one of SEQ ID NO: 57-80.

93. The vaccine of paragraph 91 or 92, wherein the 5' terminal cap is or comprises 7mG(5')ppp(5')NlmpNp.

94. The vaccine of any one of paragraphs 91-93, wherein 100% of the uracil in the open reading frame is modified to include N1-methyl pseudouridine at the 5-position of the uracil.

95. The vaccine of any one of paragraphs 91-94, wherein the vaccine is formulated in a lipid nanoparticle comprising: DLin-MC3-DMA; cholesterol; 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC); and polyethylene glycol (PEG) 2000-DMG.

96. The vaccine of paragraph 95, wherein the lipid nanoparticle further comprises trisodium citrate buffer, sucrose and water.

97. A respiratory syncytial virus (RSV) vaccine, comprising:

at least one messenger ribonucleic acid (mRNA) polynucleotide having a 5' terminal cap 7mG(5')ppp(5')NlmpNp, a sequence identified by any one of SEQ ID NO: 57-80 and a 3' polyA tail, formulated in a lipid nanoparticle comprising DLin-MC3-DMA, cholesterol, 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), and polyethylene glycol (PEG) 2000-DMG, wherein the uracil nucleotides of the sequence identified by any one of SEQ ID NO: 57-80 are modified to include N1-methyl pseudouridine at the 5-position of the uracil nucleotide.

This disclosure is not limited in its application to the details of construction and the arrangement of components set forth in the following description or illustrated in the drawings. The disclosure is capable of other embodiments and of being practiced or of being carried out in various ways. Also, the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of "including," "comprising," or "having," "containing," "involving," and variations thereof herein, is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

EXAMPLES

Example 1: Manufacture of Polynucleotides

According to the present disclosure, the manufacture of polynucleotides and/or parts or regions thereof may be accomplished utilizing the methods taught in International Publication WO2014/152027, entitled "Manufacturing Methods for Production of RNA Transcripts," the contents of which is incorporated herein by reference in its entirety.

Purification methods may include those taught in International Publication WO2014/152030 and International Publication WO2014/152031, each of which is incorporated herein by reference in its entirety.

Detection and characterization methods of the polynucleotides may be performed as taught in International Publication WO2014/144039, which is incorporated herein by reference in its entirety.

Characterization of the polynucleotides of the disclosure may be accomplished using polynucleotide mapping, reverse transcriptase sequencing, charge distribution analysis, detection of RNA impurities, or any combination of two or more of the foregoing. "Characterizing" comprises determining the RNA transcript sequence, determining the purity of the RNA transcript, or determining the charge heterogeneity of the RNA transcript, for example. Such methods are taught in, for example, International Publication WO2014/144711 and International Publication WO2014/144767, the content of each of which is incorporated herein by reference in its entirety.

Example 2: Chimeric Polynucleotide Synthesis

According to the present disclosure, two regions or parts of a chimeric polynucleotide may be joined or ligated using triphosphate chemistry. A first region or part of 100 nucleotides or less is chemically synthesized with a 5' monophosphate and terminal 3'desOH or blocked OH, for example. If the region is longer than 80 nucleotides, it may be synthesized as two strands for ligation.

If the first region or part is synthesized as a non-positionally modified region or part using in vitro transcription (IVT), conversion the 5'monophosphate with subsequent capping of the 3' terminus may follow.

Monophosphate protecting groups may be selected from any of those known in the art.

The second region or part of the chimeric polynucleotide may be synthesized using either chemical synthesis or IVT methods. IVT methods may include an RNA polymerase that can utilize a primer with a modified cap. Alternatively, a cap of up to 130 nucleotides may be chemically synthesized and coupled to the IVT region or part.

For ligation methods, ligation with DNA T4 ligase, followed by treatment with DNase should readily avoid concatenation.

The entire chimeric polynucleotide need not be manufactured with a phosphate-sugar backbone. If one of the regions or parts encodes a polypeptide, then such region or part may comprise a phosphate-sugar backbone.

Ligation is then performed using any known click chemistry, orthoclick chemistry, solulink, or other bioconjugate chemistries known to those in the art.

Synthetic Route

The chimeric polynucleotide may be made using a series of starting segments. Such segments include:

(a) a capped and protected 5' segment comprising a normal 3'OH (SEG. 1)

(b) a 5' triphosphate segment, which may include the coding region of a polypeptide and a normal 3'OH (SEG. 2)

(c) a 5' monophosphate segment for the 3' end of the chimeric polynucleotide (e.g., the tail) comprising cordycepin or no 3'OH (SEG. 3)

After synthesis (chemical or IVT), segment 3 (SEG. 3) may be treated with cordycepin and then with pyrophosphatase to create the 5' monophosphate.

Segment 2 (SEG. 2) may then be ligated to SEG. 3 using RNA ligase. The ligated polynucleotide is then purified and treated with pyrophosphatase to cleave the diphosphate.

The treated SEG.2-SEG. 3 construct may then be purified and SEG. 1 is ligated to the 5' terminus. A further purification step of the chimeric polynucleotide may be performed.

Where the chimeric polynucleotide encodes a polypeptide, the ligated or joined segments may be represented as: 5'UTR (SEG. 1), open reading frame or ORF (SEG. 2) and 3'UTR+PolyA (SEG. 3).

The yields of each step may be as much as 90-95%.

Example 3: PCR for cDNA Production

PCR procedures for the preparation of cDNA may be performed using 2×KAPA HIFI™ HotStart ReadyMix by Kapa Biosystems (Woburn, Mass.). This system includes 2× KAPA ReadyMix 12.5 μl; Forward Primer (10 μM) 0.75 μl; Reverse Primer (10 PM) 0.75 μl; Template cDNA 100 ng; and dH_2O diluted to 25.0 μl. The reaction conditions may be at 95° C. for 5 min. The reaction may be performed for 25 cycles of 98° C. for 20 sec, then 58° C. for 15 sec, then 72° C. for 45 sec, then 72° C. for 5 min, then 4° C. to termination.

The reaction may be cleaned up using Invitrogen's PURELINK™ PCR Micro Kit (Carlsbad, Calif.) per manufacturer's instructions (up to 5 μg). Larger reactions may require a cleanup using a product with a larger capacity. Following the cleanup, the cDNA may be quantified using the NANODROP™ and analyzed by agarose gel electrophoresis to confirm that the cDNA is the expected size. The cDNA may then be submitted for sequencing analysis before proceeding to the in vitro transcription reaction.

Example 4: In Vitro Transcription (IVT)

The in vitro transcription reaction generates RNA polynucleotides. Such polynucleotides may comprise a region or part of the polynucleotides of the disclosure, including chemically modified RNA (e.g., mRNA) polynucleotides. The chemically modified RNA polynucleotides can be uniformly modified polynucleotides. The in vitro transcription reaction utilizes a custom mix of nucleotide triphosphates (NTPs). The NTPs may comprise chemically modified NTPs, or a mix of natural and chemically modified NTPs, or natural NTPs.

A typical in vitro transcription reaction includes the following:

1)	Template cDNA	1.0 μg
2)	10x transcription buffer (400 mM Tris-HCl pH 8.0, 190 mM $MgCl_2$, 50 mM DTT, 10 mM Spermidine)	2.0 μl
3)	Custom NTPs (25 mM each)	0.2 μl
4)	RNase Inhibitor	20 U
5)	T7 RNA polymerase	3000 U
6)	dH_20	up to 20.0 μl. and
7)	Incubation at 37° C. for 3 hr-5 hrs.	

The crude IVT mix may be stored at 4° C. overnight for cleanup the next day. 1 U of RNase-free DNase may then be used to digest the original template. After 15 minutes of incubation at 37° C., the mRNA may be purified using Ambion's MEGACLEAR™ Kit (Austin, Tex.) following the manufacturer's instructions. This kit can purify up to 500 μg of RNA. Following the cleanup, the RNA polynucleotide may be quantified using the NanoDrop and analyzed by agarose gel electrophoresis to confirm the RNA polynucleotide is the proper size and that no degradation of the RNA has occurred.

Example 5: Enzymatic Capping

Capping of a RNA polynucleotide is performed as follows where the mixture includes: IVT RNA 60 μg-180 μg and dH_2O up to 72 μl. The mixture is incubated at 65° C. for 5 minutes to denature RNA, and then is transferred immediately to ice.

The protocol then involves the mixing of 10× Capping Buffer (0.5 M Tris-HCl (pH 8.0), 60 mM KCl, 12.5 mM $MgCl_2$) (10.0 μl); 20 mM GTP (5.0 μl); 20 mM S-Adenosyl Methionine (2.5 μl); RNase Inhibitor (100 U); 2'-O-Methyltransferase (400U); Vaccinia capping enzyme (Guanylyl transferase) (40 U); dH_2O (Up to 28 μl); and incubation at 37° C. for 30 minutes for 60 μg RNA or up to 2 hours for 180 μg of RNA.

The RNA polynucleotide may then be purified using Ambion's MEGACLEAR™ Kit (Austin, Tex.) following the manufacturer's instructions. Following the cleanup, the RNA may be quantified using the NANODROP™ (ThermoFisher, Waltham, Mass.) and analyzed by agarose gel electrophoresis to confirm the RNA polynucleotide is the proper size and that no degradation of the RNA has occurred. The RNA polynucleotide product may also be sequenced by running a reverse-transcription-PCR to generate the cDNA for sequencing.

Example 6: PolyA Tailing Reaction

Without a poly-T in the cDNA, a poly-A tailing reaction must be performed before cleaning the final product. This is

done by mixing capped IVT RNA (100 μl); RNase Inhibitor (20 U); 10× Tailing Buffer (0.5 M Tris-HCl (pH 8.0), 2.5 M NaCl, 100 mM $MgCl_2$) (12.0 μl); 20 mM ATP (6.0 μl); Poly-A Polymerase (20 U); dH_2O up to 123.5 μl and incubation at 37° C. for 30 min. If the poly-A tail is already in the transcript, then the tailing reaction may be skipped and proceed directly to cleanup with Ambion's MEGA-CLEAR™ kit (Austin, Tex.) (up to 500 μg). Poly-A Polymerase may be a recombinant enzyme expressed in yeast.

It should be understood that the processivity or integrity of the polyA tailing reaction may not always result in an exact size polyA tail. Hence, polyA tails of approximately between 40-200 nucleotides, e.g., about 40, 50, 60, 70, 80, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 150-165, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164 or 165 are within the scope of the present disclosure.

Example 7: Natural 5' Caps and 5' Cap Analogues

5'-capping of polynucleotides may be completed concomitantly during the in vitro-transcription reaction using the following chemical RNA cap analogs to generate the 5'-guanosine cap structure according to manufacturer protocols: 3'-O-Me-m7G(5')ppp(5') G [the ARCA cap];G(5')ppp(5')A; G(5')ppp(5')G; m7G(5')ppp(5')A; m7G(5')ppp(5')G (New England BioLabs, Ipswich, Mass.). 5'-capping of modified RNA may be completed post-transcriptionally using a Vaccinia Virus Capping Enzyme to generate the "Cap 0" structure: m7G(5')ppp(5')G (New England BioLabs, Ipswich, Mass.). Cap 1 structure may be generated using both Vaccinia Virus Capping Enzyme and a 2'-O methyl-transferase to generate: m7G(5')ppp(5')G-2'-O-methyl. Cap 2 structure may be generated from the Cap 1 structure followed by the 2'-O-methylation of the 5'-antepenultimate nucleotide using a 2'-O methyl-transferase. Cap 3 structure may be generated from the Cap 2 structure followed by the 2'-O-methylation of the 5'-preantepenultimate nucleotide using a 2'-0 methyl-transferase. Enzymes are preferably derived from a recombinant source.

When transfected into mammalian cells, the modified mRNAs have a stability of between 12-18 hours or more than 18 hours, e.g., 24, 36, 48, 60, 72 or greater than 72 hours.

Example 8: Capping Assays

Protein Expression Assay

Polynucleotides (e.g., mRNA) encoding a polypeptide, containing any of the caps taught herein, can be transfected into cells at equal concentrations. The amount of protein secreted into the culture medium can be assayed by ELISA at 6, 12, 24 and/or 36 hours post-transfection. Synthetic polynucleotides that secrete higher levels of protein into the medium correspond to a synthetic polynucleotide with a higher translationally-competent cap structure.

Purity Analysis Synthesis

RNA (e.g., mRNA) polynucleotides encoding a polypeptide, containing any of the caps taught herein can be compared for purity using denaturing Agarose-Urea gel electrophoresis or HPLC analysis. RNA polynucleotides with a single, consolidated band by electrophoresis correspond to the higher purity product compared to polynucleotides with multiple bands or streaking bands. Chemically modified RNA polynucleotides with a single HPLC peak also correspond to a higher purity product. The capping reaction with a higher efficiency provides a more pure polynucleotide population.

Cytokine Analysis

RNA (e.g., mRNA) polynucleotides encoding a polypeptide, containing any of the caps taught herein can be transfected into cells at multiple concentrations. The amount of pro-inflammatory cytokines, such as TNF-alpha and IFN-beta, secreted into the culture medium can be assayed by ELISA at 6, 12, 24 and/or 36 hours post-transfection. RNA polynucleotides resulting in the secretion of higher levels of pro-inflammatory cytokines into the medium correspond to a polynucleotides containing an immune-activating cap structure.

Capping Reaction Efficiency

RNA (e.g., mRNA) polynucleotides encoding a polypeptide, containing any of the caps taught herein can be analyzed for capping reaction efficiency by LC-MS after nuclease treatment. Nuclease treatment of capped polynucleotides yield a mixture of free nucleotides and the capped 5'-5-triphosphate cap structure detectable by LC-MS. The amount of capped product on the LC-MS spectra can be expressed as a percent of total polynucleotide from the reaction and correspond to capping reaction efficiency. The cap structure with a higher capping reaction efficiency has a higher amount of capped product by LC-MS.

Example 9: Agarose Gel Electrophoresis of Modified RNA or RT PCR Products

Individual RNA polynucleotides (200-400 ng in a 20 μl volume) or reverse transcribed PCR products (200-400 ng) may be loaded into a well on a non-denaturing 1.2% Agarose E-Gel (Invitrogen, Carlsbad, Calif.) and run for 12-15 minutes, according to the manufacturer protocol.

Example 10: Nanodrop Modified RNA Quantification and UV Spectral Data

Chemically modified RNA polynucleotides in TE buffer (1 μl) are used for Nanodrop UV absorbance readings to quantitate the yield of each polynucleotide from an chemical synthesis or in vitro transcription reaction.

Example 11: Formulation of Modified mRNA Using Lipidoids

RNA (e.g., mRNA) polynucleotides may be formulated for in vitro experiments by mixing the polynucleotides with the lipidoid at a set ratio prior to addition to cells. In vivo formulation may require the addition of extra ingredients to facilitate circulation throughout the body. To test the ability of these lipidoids to form particles suitable for in vivo work, a standard formulation process used for siRNA-lipidoid formulations may be used as a starting point. After formation of the particle, polynucleotide is added and allowed to integrate with the complex. The encapsulation efficiency is determined using a standard dye exclusion assays.

Example 12: Immunogenicity Study

The instant study is designed to test the immunogenicity in mice of candidate hMPV vaccines comprising a mRNA polynucleotide encoding Fusion (F) glycoprotein, major surface glycoprotein G, or a combination thereof, obtained from hMPV.

Mice are immunized intravenously (IV), intramuscularly (IM), or intradermally (ID) with candidate vaccines. Candidate vaccines are chemically modified or unmodified. A total of four immunizations are given at 3-week intervals (i.e., at weeks 0, 3, 6, and 9), and sera are collected after each immunization until weeks 33-51. Serum antibody titers against Fusion (F) glycoprotein or major surface glycoprotein (G) protein are determined by ELISA. Sera collected from each mouse during weeks 10-16 are pooled, and total IgG purified. Purified antibodies are used for immunoelectron microscopy, antibody-affinity testing, and in vitro protection assays.

Example 13: hMPV Rodent Challenge

The instant study is designed to test the efficacy in cotton rats of candidate hMPV vaccines against a lethal challenge using an hMPV vaccine comprising mRNA encoding Fusion (F) glycoprotein, major surface glycoprotein G, or a combination of both antigens obtained from hMPV. Cotton rats are challenged with a lethal dose of the hMPV.

Animals are immunized intravenously (IV), intramuscularly (IM), or intradermally (ID) at week 0 and week 3 with candidate hMPV vaccines with and without adjuvant. Candidate vaccines are chemically modified or unmodified. The animals are then challenged with a lethal dose of hMPV on week 7 via IV, IM or ID. Endpoint is day 13 post infection, death or euthanasia. Animals displaying severe illness as determined by >30% weight loss, extreme lethargy or paralysis are euthanized. Body temperature and weight are assessed and recorded daily.

In experiments where a lipid nanoparticle (LNP) formulation is used, the formulation may include a cationic lipid, non-cationic lipid, PEG lipid and structural lipid in the ratios 50:10:1.5:38.5. The cationic lipid is DLin-KC2-DMA (50 mol %) or DLin-MC3-DMA (50 mol %), the non-cationic lipid is DSPC (10 mol %), the PEG lipid is PEG-DOMG (1.5 mol %) and the structural lipid is cholesterol (38.5 mol %), for example.

Example 14: Immunogenicity of hMPV mRNA Vaccine in BALB/c Mice

The instant study was designed to test the immunogenicity in BALB/c mice of hMPV vaccines comprising an mRNA polynucleotide encoding the hMPV Fusion (F) glycoprotein. The mRNA polynucleotide encodes the full-length fusion protein and comprises the wild-type nucleotide sequence obtained from the hMPV A2a strain. Mice were divided into 3 groups (n=8 for each group) and immunized intramuscularly (IM) with PBS, a 10 μg dose of mRNA vaccines encoding hMPV fusion protein, or a 2 μg dose of mRNA vaccines encoding hMPV fusion protein. A total of two immunizations were given at 3-week intervals (i.e., at weeks 0, and 3 weeks), and sera were collected after each immunization according to the schedule described in Table 1. Serum antibody titers against hMPV fusion glycoprotein were determined by ELISA and antibodies were detected in the sera collected on day 14 onward. Both vaccine doses tested induced comparable levels of immune response in mice (FIGS. **2**A-**2**C).

Additionally, mice sera were used for IgG isotyping (FIGS. **3**A-**3**C). Both hMPV fusion protein-specific IgG1 and IgG2a were detected in mice sera. hMPV fusion protein mRNA vaccine also induced Th1 and Th2 cytokine responses, with a Th1 bias.

Sera from mice immunized with either 10 μg or 2 μg doses of the hMPV fusion protein mRNA vaccine contain neutralizing antibodies. The ability of these antibodies to neutralize hMPV B2 strain was also tested. The antibody-containing sera successfully neutralized the hMPV B2 virus (FIG. **4**).

Example 15: T-Cell Stimulation

The instant study was designed to test T-cell stimulation in the splenocytes of mice immunized with mRNA vaccines encoding hMPV fusion protein, as described herein. Immunization of BALB/c mice was performed as described in Example 14. The splenocytes for each group were pooled and split into two parts. One part of splenocytes from each group of mice was stimulated with hMPV-free media, Concanavalin A or a hMPV fusion protein peptide pool comprising 15-mers (15 amino acids long); while the other part of splenocytes from each group of mice was stimulated with hMPV-free media, Concanavalin A or inactivated hMPV virus. Secreted mouse cytokines were measured using the Meso Scale Discovery (MSD) assay.

Cytokines specific to Th1 or Th2 responses were measured. For Th1 response, IFN-γ, IL2 and IL12 were detected from splenocytes stimulated with the hMPV fusion protein peptide pool at a level comparable to that of Concanavalin A (FIGS. **5**A-**5**C). For a Th2 response, the hMPV fusion protein peptide pool induced the secretion of detectable IL10, TNF-α, IL4 and IL, but not IL5, while Concanavalin A stimulated the secretion of all the above-mentioned Th2 cytokines (FIGS. **6**A-**6**E) at a much higher level.

In contrast, inactivated hMPV virus only induced the secretion of IL2 in the Th1 response comparable to that of Concanavalin A (FIGS. **7**A-**7**C). For the Th2 response, the inactivated hMPV virus induced the secretion of detectable IL10, TNF-α, IL4 and IL6, but not IL5, while Concanavalin A stimulated the secretion of all the above-mentioned Th2 cytokines (FIGS. **8**A-**8**E) at a much higher level.

Example 16: hMPV Rodent Challenge in Cotton Rats Immunized with mRNA Vaccine Encoding hMPV Fusion Protein

The instant study was designed to test the efficacy in cotton rats of hMPV vaccines against a lethal challenge. mRNA vaccines encoding hMPV fusion protein were used. The mRNA polynucleotide encodes a full-length fusion protein and comprises the wild-type nucleotide sequence obtained from the hMPV A2a strain.

Cotton rats were immunized intramuscularly (IM) at week 0 and week 3 with the mRNA vaccines encoding hMPV fusion protein with either 2 μg or 10 μg doses for each immunization. The animals were then challenged with a lethal dose of hMPV in week 7 post initial immunization via IV, IM or ID. The endpoint was day 13 post infection, death or euthanasia. Viral titers in the noses and lungs of the cotton rats were measured. The results (FIGS. **9**A and **9**B) show that a 10 μg dose of mRNA vaccine protected the cotton mice 100% in the lung and drastically reduced the viral titer in the nose after challenge (~2 log reduction). Moreover, a 2 μg dose of mRNA vaccine showed a 1 log reduction in lung viral titer in the cotton mice challenged.

Further, the histopathology of the lungs of the cotton mice immunized and challenged showed no pathology associated with vaccine-enhanced disease (FIG. **10**).

Example 17: Immunogenicity Study

The instant study is designed to test the immunogenicity in mice of candidate PIV3 vaccines comprising a mRNA

polynucleotide encoding hemagglutinin-neuraminidase or fusion protein (F or F0) obtained from PIV3.

Mice are immunized intravenously (IV), intramuscularly (IM), or intradermally (ID) with candidate vaccines. Candidate vaccines are chemically modified or unmodified. A total of four immunizations are given at 3-week intervals (i.e., at weeks 0, 3, 6, and 9), and sera are collected after each immunization until weeks 33-51. Serum antibody titers against hemagglutinin-neuraminidase or fusion protein (F or F0) are determined by ELISA. Sera collected from each mouse during weeks 10-16 are, optionally, pooled, and total IgGs are purified. Purified antibodies are used for immuno-electron microscopy, antibody-affinity testing, and in vitro protection assays.

Example 18: PIV3 Rodent Challenge

The instant study is designed to test the efficacy in cotton rats of candidate PIV3 vaccines against a lethal challenge using a PIV3 vaccine comprising mRNA encoding hemagglutinin-neuraminidase or fusion protein (F or F0) obtained from PIV3. Cotton rats are challenged with a lethal dose of the PIV3.

Animals are immunized intravenously (IV), intramuscularly (IM), or intradermally (ID) at week 0 and week 3 with candidate PIV3 vaccines with and without adjuvant. Candidate vaccines are chemically modified or unmodified. The animals are then challenged with a lethal dose of PIV3 on week 7 via IV, IM or ID. Endpoint is day 13 post infection, death or euthanasia. Animals displaying severe illness as determined by >30% weight loss, extreme lethargy or paralysis are euthanized. Body temperature and weight are assessed and recorded daily.

In experiments where a lipid nanoparticle (LNP) formulation is used, the formulation may include a cationic lipid, non-cationic lipid, PEG lipid and structural lipid in the ratios 50:10:1.5:38.5. The cationic lipid is DLin-KC2-DMA (50 mol %) or DLin-MC3-DMA (50 mol %), the non-cationic lipid is DSPC (10 mol %), the PEG lipid is PEG-DOMG (1.5 mol %) and the structural lipid is cholesterol (38.5 mol %), for example.

Example 19: hMPV/PIV Cotton Rat Challenge

The instant study was designed to test the efficacy in cotton rats of candidate hMPV mRNA vaccines, PIV3 mRNA vaccines, or hMPV/PIV combination mRNA vaccines against a lethal challenge using PIV3 strain or hMPV/A2 strain. The study design is shown in Table 9.

Cotton rats of 10-12 weeks old were divided into 12 groups (n=5), and each group was vaccinated with mRNA vaccines indicated in Table 9. The PIV3 vaccine comprises mRNA encoding hemagglutinin-neuraminidase or fusion protein (F or F0) obtained from PIV3. The hMPV mRNA vaccine encodes the full-length hMPV fusion protein. The hMPV/PIV combination mRNA vaccine is a mixture of the PIV3 vaccine and hMPV vaccine at a 1:1 ratio.

Cotton rats were immunized intramuscularly (IM) at week 0 and week 3 with candidate vaccines with the doses indicated in Table 9. Cotton rats immunized with hMPV mRNA vaccines or hMPV/PIV combination mRNA vaccines were challenged with a lethal dose of hMPV/A2 strain on week 7 via IM. Cotton rats immunized with PIV mRNA vaccines or hMPV/PIV combination mRNA vaccines were challenged with a lethal dose of PIV3 strain on week 7 via IM.

The endpoint was day 13 post infection, death or euthanasia. Animals displaying severe illness as determined by >30% weight loss, extreme lethargy or paralysis were euthanized. Body temperature and weight were assessed and recorded daily.

Lung and nose hMPV/A2 (FIG. **12**) or PIV3 (FIG. **13**) viral titers were assessed. Lung histopathology of the immunized and challenged cotton rat immunized and challenged were assessed to determine pathology associated with vaccine enhance disease. Neutralization antibody titers in the serum of immunized cotton rats on day 0 and 42 post immunization were assessed (FIG. **11**).

hMPV/A2 (FIG. **14**) or PIV3 (FIG. **15**) neutralizing antibody titers in the serum samples of the immunized cotton rat 42 days post immunization were measured. All mRNA vaccines tested induced strong neutralizing antibodies cotton rats. Lung histopathology of the immunized cotton rats were also evaluated (FIG. **16**). Low occurrence of alevolitis and interstitial pneumonia was observed, indicating no antibody-dependent enhancement (ADE) of hMPV or PIV associated diseases.

Example 20: Betacoronavirus Immunogenicity Study

The instant study is designed to test the immunogenicity in rabbits of candidate betacoronavirus (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1 or a combination thereof) vaccines comprising a mRNA polynucleotide encoding the spike (S) protein, the S1 subunit (S1) of the spike protein, or the S2 subunit (S2) of the spike protein obtained from a betacoronavirus (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1).

Rabbits are vaccinated on week 0 and 3 via intravenous (IV), intramuscular (IM), or intradermal (ID) routes. One group remains unvaccinated and one is administered inactivated betacoronavirus. Serum is collected from each rabbit on weeks 1, 3 (pre-dose) and 5. Individual bleeds are tested for anti-S, anti-S1 or anti-S2 activity via a virus neutralization assay from all three time points, and pooled samples from week 5 only are tested by Western blot using inactivated betacoronavirus (e.g., inactivated MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1).

In experiments where a lipid nanoparticle (LNP) formulation is used, the formulation may include a cationic lipid, non-cationic lipid, PEG lipid and structural lipid in the ratios 50:10:1.5:38.5. The cationic lipid is DLin-KC2-DMA (50 mol %) or DLin-MC3-DMA (50 mol %), the non-cationic lipid is DSPC (10 mol %), the PEG lipid is PEG-DOMG (1.5 mol %) and the structural lipid is cholesterol (38.5 mol %), for example.

Example 21: Betacoronavirus Challenge

The instant study is designed to test the efficacy in rabbits of candidate betacoronavirus (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-HKU1 or a combination thereof) vaccines against a lethal challenge using a betacoronavirus (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-HKU1 or a combination thereof) vaccine comprising mRNA encoding the spike (S) protein, the S1 subunit (S1) of the spike protein, or the S2 subunit (S2) of the spike protein obtained from betacoronavirus (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL,

HCoV-NH or HCoV-HKU1). Rabbits are challenged with a lethal dose (10×LD90; ~100 plaque-forming units; PFU) of betacoronavirus (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1).

The animals used are 6-8 week old female rabbits in groups of 10. Rabbits are vaccinated on weeks 0 and 3 via an IM, ID or IV route of administration. Candidate vaccines are chemically modified or unmodified. Rabbit serum is tested for microneutralization (see Example 14). Rabbits are then challenged with ~1 LD90 of betacoronavirus (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1) on week 7 via an IN, IM, ID or IV route of administration. Endpoint is day 13 post infection, death or euthanasia. Animals displaying severe illness as determined by >30% weight loss, extreme lethargy or paralysis are euthanized. Body temperature and weight are assessed and recorded daily.

Example 22: Microneutralization Assay

Nine serial 2-fold dilutions (1:50-1:12,800) of rabbit serum are made in 50 μl virus growth medium (VGM) with trypsin in 96 well microtiter plates. Fifty microliters of virus containing ~50 pfu of betacoronavirus (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1) is added to the serum dilutions and allowed to incubate for 60 minutes at room temperature (RT). Positive control wells of virus without sera and negative control wells without virus or sera are included in triplicate on each plate. While the serum-virus mixtures incubate, a single cell suspension of Madin-Darby Canine-Kidney cells are prepared by trypsinizing (Gibco 0.5% bovine pancrease trypsin in EDTA) a confluent monolayer and suspended cells are transferred to a 50 ml centrifuge tube, topped with sterile PBS and gently mixed. The cells are then pelleted at 200 g for 5 minutes, supernatant aspirated and cells resuspended in PBS. This procedure is repeated once and the cells are resuspended at a concentration of 3×10^5/ml in VGM with porcine trypsin. Then, 100 μl of cells are added to the serum-virus mixtures and the plates incubated at 35° C. in C02 for 5 days. The plates are fixed with 80% acetone in phosphate buffered saline (PBS) for 15 minutes at RT, air dried and then blocked for 30 minutes containing PBS with 0.5% gelatin and 2% FCS. An antibody to the S proteins, S1 protein or S2 protein is diluted in PBS with 0.5% gelatin/2% FCS/0.5% Tween 20 and incubated at RT for 2 hours. Wells are washed and horseradish peroxidase-conjugated goat anti-mouse IgG added, followed by another 2 hour incubation. After washing, O-phenylenediamine dihydrochloride is added and the neutralization titer is defined as the titer of serum that reduced color development by 50% compared to the positive control wells.

Example 23: MERS CoV Vaccine Immunogenicity Study in Mice

The instant study was designed to test the immunogenicity in mice of candidate MERS-CoV vaccines comprising a mRNA polynucleotide encoding the full-length Spike (S) protein, or the S2 subunit (S2) of the Spike protein obtained from MERS-CoV.

Mice were vaccinated with a 10 μg dose of MERS-CoV mRNA vaccine encoding either the full-length MERS-CoV Spike (S) protein, or the S2 subunit (S2) of the Spike protein on days 0 and 21. Sera were collected from each mice on days 0, 21, 42, and 56. Individual bleeds were tested for anti-S, anti-S2 activity via a virus neutralization assay from all four time points.

As shown in FIG. **17**, the MERS-CoV vaccine encoding the full-length S protein induced strong immune response after the boost dose on day 21. Further, full-length S protein vaccine generated much higher neutralizing antibody titers as compared to S2 alone (FIG. **18**).

Example 24: MERS CoV Vaccine Immunogenicity Study in New Zealand White Rabbits

The instant study was designed to test the immunogenicity of candidate MERS-CoV mRNA vaccines encoding the full-length Spike (S) protein. The New Zealand white rabbits used in this study weighed about 4-5 kg. The rabbits were divided into three groups (Group 1a, Group 1b, and Group 2, n=8). Rabbits in Group 1a were immunized intramuscularly (IM) with one 20 μg dose of the MERS-CoV mRNA vaccine encoding the full-length Spike protein on day 0. Rabbits in Group 1b were immunized intramuscularly (IM) with one 20 μg dose of the MERS-CoV mRNA vaccine encoding the full-length Spike protein on day 0, and again on day 21 (booster dose). Group 2 received placebo (PBS). The immunized rabbits were then challenged and samples were collected 4 days after challenge. The viral loads in the lungs, bronchoalveolar lavage (Bal), nose, and throat of the rabbits were determined, e.g., via quantitative PCR. Replicating virus in the lung tissues of the rabbits were also detected. Lung histopathology were evaluated and the neutralizing antibody titers in serum samples of the rabbits were determined.

Two 20 μg doses of MERS-CoV mRNA vaccine resulted in a 3 log reduction of viral load in the nose and led to complete protection in the throat of the New Zealand white rabbits (FIG. **19**A). Two 20 μg doses of MERS-CoV mRNA vaccine also resulted in a 4 log reduction of viral load in the BAL of the New Zealand white rabbits (FIG. **19**B). One 20 μg dose of MERS-CoV mRNA vaccine resulted in a 2 log reduction of viral load, while two 20 μg doses of MERS-CoV mRNA vaccine resulted in an over 4 log reduction of viral load in the lungs of the New Zealand white rabbits (FIG. **19**C).

Quantitative PCR results show that two 20 μg doses of MERS-CoV mRNA vaccine reduced over 99% (2 log) of viruses in the lungs of New Zealand white rabbits (FIG. **20**A). No replicating virus were detected in the lungs (FIG. **20**B).

Further, as shown in FIG. **21**, two 20 μg doses of MERS-CoV mRNA vaccine induced significant amount of neutralizing antibodies against MERS-CoV (ECso between 500-1000).

The MERS-CoV mRNA vaccine induced antibody titer is 3-5 fold better than any other vaccines tested in the same model.

Example 25: Immunogenicity Study

The instant study is designed to test the immunogenicity in mice of candidate MeV vaccines comprising a mRNA polynucleotide encoding MeV hemagglutinin (HA) protein, MeV Fusion (F) protein or a combination of both.

Mice are immunized intravenously (IV), intramuscularly (IM), or intradermally (ID) with candidate vaccines. Up to three immunizations are given at 3-week intervals (i.e., at weeks 0, 3, 6, and 9), and sera are collected after each

immunization until weeks 33-51. Serum antibody titers against MeV HA protein or MeV F protein are determined by ELISA.

Example 26: MeV Rodent Challenge

The instant study is designed to test the efficacy in transgenic mice of candidate MeV vaccines against a lethal challenge using a MeV vaccine comprising mRNA encoding MeV HA protein or MeV F protein. The transgenic mice express human receptor CD46 or signaling lymphocyte activation molecule (SLAM) (also referred to as CD150). Humans are the only natural host for MeV infection, thus transgenic lines are required for this study. CD46 is a complement regulatory protein that protects host tissue from complement deposition by binding to complement components C3b and C4b. Its expression on murine fibroblast and lymphoid cell lines renders these otherwise refractory cells permissive for MeV infection, and the expression of CD46 on primate cells parallels the clinical tropism of MeV infection in humans and nonhuman primates (Rall G F et al. *PNAS USA* 1997; 94(9):4659-63). SLAM is a type 1 membrane glycoprotein belonging to the immunoglobulin superfamily. It is expressed on the surface of activated lymphocytes, macrophages, and dendritic cells and is thought to play an important role in lymphocyte signaling. SLAM is a receptor for both wild-type and vaccine MeV strains (Sellin C I et al. *J Virol.* 2006; 80(13):6420-29).

CD46 or SLAM/CD150 transgenic mice are challenged with a lethal dose of the MeV. Animals are immunized intravenously (IV), intramuscularly (IM), or intradermally (ID) at week 0 and week 3 with candidate MeV vaccines with and without adjuvant. The animals are then challenged with a lethal dose of MeV on week 7 via IV, IM or ID. Endpoint is day 13 post infection, death or euthanasia. Animals displaying severe illness as determined by >30% weight loss, extreme lethargy or paralysis are euthanized. Body temperature and weight are assessed and recorded daily.

In experiments where a lipid nanoparticle (LNP) formulation is used, the formulation may include a cationic lipid, non-cationic lipid, PEG lipid and structural lipid in the ratios 50:10:1.5:38.5. The cationic lipid is DLin-KC2-DMA (50 mol %), the non-cationic lipid is DSPC (10 mol %), the PEG lipid is PEG-DOMG (1.5 mol %) and the structural lipid is cholesterol (38.5 mol %), for example.

TABLE 1

hMPV Immunogenicity studies bleeding schedule

	Animal groups		Day							
	(n = 8)	vaccine	−2	0	7	14	21	28	35	56
Placebo	Group 1 (n = 8)	PBS (IM)	Pre-Bleed	Prime	Bleeds	Bleeds	Bleeds/Boost	Bleeds	Bleeds	Harvest Spleens/Terminal Bleeds
10 μg Dose	Group 2 (n = 8)	10 μg (IM)								
2 μg Dose	Group 3 (n = 8)	2 μg (IM)								

Total n = 24

Each of the sequences described herein encompasses a chemically modified sequence or an unmodified sequence which includes no nucleotide modifications.

TABLE 2

hMPV Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
gi|122891979|gb|EF051124.1| Human metapneumovirus isolate TN/92-4 fusion protein gene, complete genome	ATGAGCTGGAAGGTGGTGATTATCTTCAGCCTGCTGATTA CACCTCAACACGGCCTGAAGGAGAGCTACCTGGAAGAGA GCTGCTCCACCATCACCGAGGGCTACCTGAGCGTGCTGC GGACCGGCTGGTACACCAACGTGTTCACCCTGGAGGTGG GCGACGTGGAGAACCTGACCTGCAGCGACGGCCCTAGCC TGATCAAGACCGAGCTGGACCTGACCAAGAGCGCTCTGA GAGAGCTGAAGACCGTGTCCGCCGACCAGCTGGCCAGAG AGGAACAGATCGAGAACCCTCGGCAGAGCAGATTCGTGC TGGGCGCCATCGCTCTGGGAGTCGCCGCTGCCGCTGCAG TGACAGCTGGAGTGGCCATTGCTAAGACCATCAGACTGG AAAGCGAGGTGACAGCCATCAACAATGCCCTGAAGAAG ACCAACGAGGCCGTGAGCACCCTGGGCAATGGAGTGAGA GTGCTGGCCACAGCCGTGCGGGAGCTGAAGGACTTCGTG AGCAAGAACCTGACCAGAGCCATCAACAAGAACAAGTG CGACATCGATGACCTGAAGATGGCCGTGAGCTTCTCCCA GTTCAACAGACGGTTCCTGAACGTGGTGAGACAGTTCTC CGACAACGCTGGAATCACACCTGCCATTAGCCTGGACCT GATGACCGACGCCGAGCTGGCTAGAGCCGTGCCCAACAT GCCCACCAGCGCTGGCCAGATCAAGCTGATGCTGGAGAA CAGAGCCATGGTGCGGAGAAAGGGCTTCGGCATCCTGAT TGGGGTGTATGGAAGCTCCGTGATCTACATGGTGCAGCT GCCCATCTTCGGCGTGATCGACACACCCTGCTGGATCGTG	1

TABLE 2-continued

hMPV Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
	AAGGCCGCTCCTAGCTGCTCCGAGAAGAAAGGAAACTAT	
	GCCTGTCTGCTGAGAGAGGACCAGGGCTGGTACTGCCAG	
	AACGCCGGAAGCACAGTGTACTATCCCAACGAGAAGGAC	
	TGCGAGACCAGAGGCGACCACGTGTTCTGCGACACCGCT	
	GCCGGAATCAACGTGGCCGAGCAGAGCAAGGAGTGCAA	
	CATCAACATCAGCACAACCAACTACCCCTGCAAGGTGAG	
	CACCGGACGGCACCCCATCAGCATGGTGGCTCTGAGCCC	
	TCTGGGCGCTCTGGTGGCCTGCTATAAGGGCGTGTCCTGT	
	AGCATCGGCAGCAATCGGGTGGGCATCATCAAGCAGCTG	
	AACAAGGGATGCTCCTACATCACCAACCAGGACGCCGAC	
	ACCGTGACCATCGACAACACCGTGTACCAGCTGAGCAAG	
	GTGGAGGGCGAGCAGCACGTGATCAAGGGCAGACCCGT	
	GAGCTCCAGCTTCGACCCCATCAAGTTCCCTGAGGACCA	
	GTTCAACGTGGCCCTGGACCAGGTGTTTGAGAACATCGA	
	GAACAGCCAGGCCCTGGTGGACCAGAGCAACAGAATCCT	
	GTCCAGCGCTGAGAAGGGCAACACCGGCTTCATCATTGT	
	GATCATTCTGATCGCCGTGCTGGGCAGCTCCATGATCCTG	
	GTGAGCATCTTCATCATTATCAAGAAGACCAAGAAACCC	
	ACCGGAGCCCCTCCTGAGCTGAGCGGCGTGACCAACAAT	
	GGCTTCATTCCCCACAACTGA	
gb|AY525843.1|: 3065-4684 Human metapneumovirus isolate NL/1/99, complete genome	ATGTCTTGGAAAGTGATGATCATCATTTCGTTACTCATAA	2
	CACCCCAGCACGGGCTAAAGGAGAGTTATTTGGAAGAAT	
	CATGTAGTACTATAACTGAGGGATACCTCAGTGTTTTAAG	
	AACAGGCTGGTACACTAATGTCTTCACATTAGAAGTTGGT	
	GATGTTGAAAATCTTACATGTACTGATGGACCTAGCTTAA	
	TCAAAACAGAACTTGATCTAACAAAAAGTGCTTTAAGGG	
	AACTCAAAACAGTCTCTGCTGATCAGTTGGCGAGAGAGG	
	AGCAAATTGAAAATCCCAGACAATCAAGATTTGTCTTAG	
	GTGCGATAGCTCTCGGAGTTGCTACAGCAGCAGCAGTCA	
	CAGCAGGCATTGCAATAGCCAAAACCATAAGGCTTGAGA	
	GTGAGGTGAATGCAATTAAAGGTGCTCTCAAACAAACTA	
	ATGAAGCAGTATCCACATTAGGGAATGGTGTGCGGGTCC	
	TAGCCACTGCAGTGAGAGAGCTAAAAGAATTTGTGAGCA	
	AAAACCTGACTAGTGCAATCAACAGGAACAAATGTGACA	
	TTGCTGATCTGAAGATGGCTGTCAGCTTCAGTCAATTCAA	
	CAGAAGATTTCTAAATGTTGTGCGGCAGTTTTCAGACAAT	
	GCAGGGATAACACCAGCAATATCATTGGACCTGATGACT	
	GATGCTGAGTTGGCCAGAGCTGTATCATACATGCCAACA	
	TCTGCAGGGCAGATAAAACTGATGTTGGAGAACCGCGCA	
	ATGGTAAGGAGAAAAGGATTTGGAATCCTGATAGGGGTC	
	TACGGAAGCTCTGTGATTTACATGGTTCAATTGCCGATCT	
	TTGGTGTCATAGATACACCTTGTTGGATCATCAAGGCAGC	
	TCCCTCTTGCTCAGAAAAAAACGGGAATTATGCTTGCCTC	
	CTAAGAGAGGATCAAGGGTGGTATTGTAAAAATGCAGGA	
	TCTACTGTTTACTACCCAAATGAAAAAGACTGCGAAACA	
	AGAGGTGATCATGTTTTTTGTGACACAGCAGCAGGGATC	
	AATGTTGCTGAGCAATCAAGAGAATGCAACATCAACATA	
	TCTACTACCAACTACCCATGCAAAGTCAGCACAGGAAGA	
	CACCCTATAAGCATGGTTGCACTATCACCTCTCGGTGCTT	
	TGGTGGCTTGCTATAAAGGGGTAAGCTGCTCGATTGGCA	
	GCAATTGGGT	
	TGGAATCATCAAACAATTACCCAAAGGCTGCTCATACAT	
	AACCAACCAGGATGCAGACACTGTAACAATTGACAATAC	
	CGTGTATCAACTAAGCAAAGTTGAAGGTGAACAGCATGT	
	AATAAAAGGGAGACCAGTTTCAAGCAGTTTTGATCCAAT	
	CAAGTTTCCTGAGGATCAGTTCAATGTTGCGCTTGATCAA	
	GTCTTCGAAAGCATTGAGAACAGTCAGGCACTAGTGGAC	
	CAGTCAAACAAAATTCTAAACAGTGCAGAAAAAGGAAA	
	CACTGGTTTCATTATCGTAGTAATTTTGGTTGCTGTTCTTG	
	GTCTAACCATGATTTCAGTGAGCATCATCATCATAATCAA	
	GAAAACAAGGAAGCCCACAGGAGCACCTCCAGAGCTGA	
	ATGGTGTCACCAACGGCGGTTTCATACCACATAGTTA	
gb|KJ627414.1|: 3015-4634 Human metapneumovirus strain hMPV/*Homo sapiens*/PER/CFI0497/2010/B, complete genome	ATGTCTTGGAAAGTGATGATTATCATTTCGTTACTCATAA	3
	CACCTCAGCATGGACTAAAAGAAAGTTATTTAGAAGAAT	
	CATGTAGTACTATAACTGAAGGATATCTCAGTGTTTTAAG	
	AACAGGTTGGTACACCAATGTCTTTACATTAGAAGTTGGT	
	GATGTTGAAAATCTTACATGTACTGATGGACCTAGCTTAA	
	TCAAAACAGAACTTGACCTAACCAAAAGTGCTTTAAGAG	
	AACTCAAAACAGTTTCTGCTGATCAGTTAGCGAGAGAAG	
	AACAAATTGAAAATCCCAGACAATCAAGGTTTGTCCTAG	
	GTGCAATAGCTCTTGGAGTTGCCACAGCAGCAGCAGTCA	
	CAGCAGGCATTGCAATAGCCAAAACTATAAGGCTTGAGA	
	GTGAAGTGAATGCAATCAAAGGTGCTCTCAAAACAACCA	

TABLE 2-continued

hMPV Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
	ATGAGGCAGTATCAACACTAGGAAATGGAGTGCGGGTCC	
	TAGCCACTGCAGTAAGAGAGCTGAAAGAATTTGTGAGCA	
	AAAACCTGACTAGTGCGATCAACAAGAACAAGTGTGACA	
	TTGCTGATTTGAAGATGGCTGTCAGCTTCAGTCAGTTCAA	
	CAGAAGATTCCTAAATGTTGTGCGGCAGTTTTCAGACAAT	
	GCAGGGATAACACCAGCAATATCATTGGACCTGATGAAT	
	GATGCTGAGCTGGCCAGAGCTGTATCATACATGCCAACA	
	TCTGCAGGACAGATAAAACTAATGTTAGAGAACCGTGCA	
	ATGGTGAGGAGAAAAGGATTTGGAATCTTGATAGGGGTC	
	TACGGAAGCTCTGTGATTTACATGGTCCAGCTGCCGATCT	
	TTGGTGTCATAAATACACCTTGTTGGATAATCAAGGCAGC	
	TCCCTCTTGTTCAGAAAAAGATGGAAATTATGCTTGCCTC	
	CTAAGAGAGGATCAAGGGTGGTATTGTAAAAATGCAGGA	
	TCCACTGTTTACTACCCAAATGAAAAAGACTGCGAAACA	
	AGAGGTGATCATGTTTTTTGTGACACAGCAGCAGGGATC	
	AATGTTGCTGAGCAATCAAGAGAATGCAACATCAACATA	
	TCTACCACCAACTACCCATGCAAAGTCAGCACAGGAAGA	
	CACCCTATCAGCATGGTTGCACTATCACCTCTCGGTGCTT	
	TGGTAGCTTGCTACAAAGGGGTTAGCTGCTCGACTGGCA	
	GTAATCAGGTTGGAATAATCAAACAACTACCTAAAGGCT	
	GCTCATACATAACTAACCAGGACGCAGACACTGTAACAA	
	TTGACAACACTGTGTATCAACTAAGCAAAGTTGAGGGTG	
	AACAGCATGTAATAAAAGGGAGACCAGTTTCAAGCAGTT	
	TTGATCCAATCAGGTTTCCTGAGGATCAGTTCAATGTTGC	
	GCTTGATCAAGTCTTTGAAAGCATTGAAAACAGTCAAGC	
	ACTAGTGGACCAGTCAAACAAAATTCTGAACAGTGCAGA	
	AAAAGGAAACACTGGT	
	TTCATTATTGTAATAATTTTGATTGCTGTTCTTGGGTTAAC	
	CATGATTTCAGTGAGCATCATCATCATAATCAAAAAAAC	
	AAGGAAGCCCACAGGGGCACCTCCGGAGCTGAATGGTGT	
	TACCAACGGCGGTTTCATACCGCATAGTTAG	
gb|KJ723483.1|: 5586-7310 Human respiratory syncytial virus strain RSVA/*Homo sapiens*/USA/84I-215A-01/1984, complete genome	ATGGAGTTGCCAATCCTCAAAACAAATGCAATTACCACA	4
	ATCCTTGCTGCAGTCACACTCTGTTTCGCTTCCAGTCAAA	
	ACATCACTGAAGAATTTTATCAATCAACATGCAGTGCAG	
	TTAGCAAAGGCTATCTTAGTGCTCTAAGAACTGGTTGGTA	
	TACTAGTGTTATAACTATAGAATTAAGTAATATCAAGGA	
	AAATAAGTGTAATGGAACAGATGCTAAGGTAAAATTGAT	
	AAAACAAGAATTAGATAAATATAAAAATGCTGTAACAGA	
	ATTGCAGTTGCTCATGCAAAGCACACCAGCAGCCAACAA	
	TCGAGCCAGAAGAGAACTACCAAGGTTTATGAATTATAC	
	ACTCAATAATACCAAAAATACCAATGTAACATTAAGCAA	
	GAAAAGGAAAAGAAGATTTCTTGGCTTTTTGTTAGGTGTT	
	GGATCTGCAATCGCCAGTGGCATTGCTGTATCTAAGGTCC	
	TGCACCTAGAAGGGGAAGTGAACAAAATCAAAAGTGCTC	
	TACTATCCACAAACAAGGCTGTAGTCAGCTTATCAAATG	
	GAGTTAGTGTCTTAACCAGCAAAGTGTTAGACCTCAAAA	
	ACTATATAGATAAACAGTTGTTACCTATTGTGAACAAGC	
	AAAGCTGCAGCATATCAAACATTGAAACTGTGATAGAGT	
	TCCAACAAAAGAACAACAGACTACTAGAGATTACCAGGG	
	AATTTAGTGTTAATGCAGGTGTAACTACACCTGTAAGCAC	
	TTATATGTTAACTAATAGTGAATTATTATCATTAATCAAT	
	GATATGCCTATAACAAATGATCAGAAAAAGTTAATGTCC	
	AACAATGTTCAAATAGTTAGACAGCAAAGTTACTCTATC	
	ATGTCCATAATAAAGGAGGAAGTCTTAGCATATGTAGTA	
	CAATTACCACTATATGGTGTAATAGATACACCCTGTTGGA	
	AACTGCACACATCCCCTCTATGTACAACCAACACAAAGG	
	AAGGGTCCAACATCTGCTTAACAAGAACCGACAGAGGAT	
	GGTATTGTGACAATGCAGGATCAGTATCTTTCTTCCCACA	
	AGCTGAAACATGTAAAGTTCAATCGAATCGGGTATTTTGT	
	GACACAATGAACAGTTTAACATTACCAAGTGAAGTAAAT	
	CTCTGCAACATTGACATATTCAACCCCAAATATGATTGCA	
	AAATTATGACTTCAAAAACAGATGTAAGCAGCTCCGTTA	
	TCACATCTCTAGGAGCCATTGTGTCATGCTATGGCAAAAC	
	TAAATGTACAGCATCCAATAAAAATCGTGGGATCATAAA	
	GACATTTTCTAACGGGTGTGATTATGTATCAAATAAGGG	
	GGTGGATACTGTGTCTGTAGGTAATACATTATATTATGTA	
	AATAAGCAAGAAGGCAAAAGTCTCTATGTAAAAGGTGAA	
	CCAATAATAAATTTCTATGACCCATTAGTGTTCCCCTCTG	
	ATGAATTTGATGCATCAATATCTCAAGTCAATGAGAAGA	
	TTAACCAGAGCCTAGCATTTATTCGTAAATCCGATGAATT	
	ATTACATAATGTAAATGCTGGTAAATCCACCACAAATAT	
	CATGATAACTACTATAATTATAGTGATTATAGTAATATTG	
	TTATCATTAATTGCAGTTGGACTGCTCCTATACTGCAAGG	
	CCAGAAGCACACCAGTCACACTAAGTAAGGATCAACTGA	

TABLE 2-continued

hMPV Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
	GTGGTATAAATAATATTGCATTTAGTAACTGA	
	hMPV mRNA Sequences	
gi|122891979|gb|EF051124.1| Human metapneumo virus isolate TN/92-4 fusion protein gene, complete genome	AUGAGCUGGAAGGUGGUGAUUAUCUUCAGCCUGCUGAU UACACCUCAACACGGCCUGAAGGAGAGCUACCUGGAAG AGAGCUGCUCCACCAUCACCGAGGGCUACCUGAGCGUG CUGCGGACCGGCUGGUACACCAACGUGUUCACCCUGGA GGUGGGCGACGUGGAGAACCUGACCUGCAGCGACGGCC CUAGCCUGAUCAAGACCGAGCUGGACCUGACCAAGAGC GCUCUGAGAGAGCUGAAGACCGUGUCCGCCGACCAGCU GGCCAGAGAGGAACAGAUCGAGAACCCUCGGCAGAGCA GAUUCGUGCUGGGCGCCAUCGCUCUGGGAGUCGCCGCU GCCGCUGCAGUGACAGCUGGAGUGGCCAUUGCUAAGAC CAUCAGACUGGAAAGCGAGGUGACAGCCAUCAACAAUG CCCUGAAGAAGACCAACGAGGCCGUGAGCACCCUGGGC AAUGGAGUGAGAGUGCUGGCCACAGCCGUGCGGGAGCU GAAGGACUUCGUGAGCAAGAACCUGACCAGAGCCAUCA ACAAGAACAAGUGCGACAUCGAUGACCUGAAGAUGGCC GUGAGCUUCUCCCAGUUCAACAGACGGUUCCUGAACGU GGUGAGACAGUUCUCCGACAACGCUGGAAUCACACCUG CCAUUAGCCUGGACCUGAUGACCGACGCCGAGCUGGCU AGAGCCGUGCCCAACAUGCCCACCAGCGCUGGCCAGAU CAAGCUGAUGCUGGAGAACAGAGCCAUGGUGCGGAGAA AGGGCUUCGGCAUCCUGAUUGGGGUGUAUGGAAGCUCC GUGAUCUACAUGGUGCAGCUGCCCAUCUUCGGCGUGAU CGACACACCCUGCUGGAUCGUGAAGGCCGCUCCUAGCU GCUCCGAGAAGAAAGGAAACUAUGCCUGUCUGCUGAGA GAGGACCAGGGCUGGUACUGCCAGAACGCCGGAAGCAC AGUGUACUAUCCCAACGAGAAGGACUGCGAGACCAGAG GCGACCACGUGUUCUGCGACACCGCUGCCGGAAUCAAC GUGGCCGAGCAGAGCAAGGAGUGCAACAUCAACAUCAG CACAACCAACUACCCCUGCAAGGUGAGCACCGGACGGC ACCCCAUCAGCAUGGUGGCUCUGAGCCCUCUGGGCGCU CUGGUGGCCUGCUAUAAGGGCGUGUCCUGUAGCAUCGG CAGCAAUCGGGUGGGCAUCAUCAAGCAGCUGAACAAGG GAUGCUCCUACAUCACCAACCAGGACGCCGACACCGUG ACCAUCGACAACACCGUGUACCAGCUGAGCAAGGUGGA GGGCGAGCAGCACGUGAUCAAGGGCAGACCCGUGAGCU CCAGCUUCGACCCCAUCAAGUUCCCUGAGGACCAGUUC AACGUGGCCCUGGACCAGGUGUUUGAGAACAUCGAGAA CAGCCAGGCCCUGGUGGACCAGAGCAACAGAAUCCUGU CCAGCGCUGAGAAGGGCAACACCGGCUUCAUCAUUGUG AUCAUUCUGAUCGCCGUGCUGGGCAGCUCCAUGAUCCU GGUGAGCAUCUUCAUCAUUAUCAAGAAGACCAAGAAAC CCACCGGAGCCCCUCCUGAGCUGAGCGGCGUGACCAAC AAUGGCUUCAUUCCCCACAACUGA	57
gb|AY525843.1|: 3065-4684 Human metapneumovirus isolate NL/1/99, complete genome	AUGUCUUGGAAAGUGAUGAUCAUCAUUUCGUUACUCAU AACACCCCAGCACGGGCUAAAGGAGAGUUAUUUGGAAG AAUCAUGUAGUACUAUAACUGAGGGAUACCUCAGUGUU UUAAGAACAGGCUGGUACACUAAUGUCUUCACAUUAGA AGUUGGUGAUGUUGAAAAUCUUACAUGUACUGAUGGA CCUAGCUUAAUCAAAACAGAACUUGAUCUAACAAAAAG UGCUUUAAGGGAACUCAAAACAGUCUCUGCUGAUCAGU UGGCGAGAGAGGAGCAAAUUGAAAAUCCCAGACAAUCA AGAUUUGUCUUAGGUGCGAUAGCUCUCGGAGUUGCUAC AGCAGCAGCAGUCACAGCAGGCAUUGCAAUAGCCAAAA CCAUAAGGCUUGAGAGUGAGGUGAAUGCAAUUAAAGG UGCUCUCAAACAAACUAAUGAAGCAGUAUCCACAUUAG GGAAUGGUGUGCGGGUCCUAGCCACUGCAGUGAGAGAG CUAAAAGAAUUUGUGAGCAAAAACCUGACUAGUGCAAU CAACAGGAACAAAUGUGACAUUGCUGAUCUGAAGAUGG CUGUCAGCUUCAGUCAAUUCAACAGAAGAUUUCUAAAU GUUGUGCGGCAGUUUUCAGACAAUGCAGGGAUAACACC AGCAAUAUCAUUGGACCUGAUGACUGAUGCUGAGUUGG CCAGAGCUGUAUCAUACAUGCCAACAUCUGCAGGGCAG AUAAAACUGAUGUUGGAGAACCGCGCAAUGGUAAGGAG AAAAGGAUUUGGAAUCCUGAUAGGGGUCUACGGAAGCU CUGUGAUUUACAUGGUUCAAUUGCCGAUCUUUGGUGUC AUAGAUACACCUUGUUGGAUCAUCAAGGCAGCUCCCUC UUGCUCAGAAAAAAACGGGAAUUAUGCUUGCCUCCUAA GAGAGGAUCAAGGGUGGUAUUGUAAAAAUGCAGGAUC UACUGUUUACUACCCAAAUGAAAAAGACUGCGAAACAA GAGGUGAUCAUGUUUUUUGUGACACAGCAGCAGGGAUC	58

TABLE 2-continued

hMPV Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
	AAUGUUGCUGAGCAAUCAAGAGAAUGCAACAUCAACAU AUCUACUACCAACUACCCAUGCAAAGUCAGCACAGGAA GACACCCUAUAAGCAUGGUUGCACUAUCACCUCUCGGU GCUUUGGUGGCUUGCUAUAAAGGGGUAAGCUGCUCGAU UGGCAGCAAUUGGGU UGGAAUCAUCAAACAAUUACCCAAAGGCUGCUCAUACA UAACCAACCAGGAUGCAGACACUGUAACAAUUGACAAU ACCGUGUAUCAACUAAGCAAAGUUGAAGGUGAACAGCA UGUAAUAAAAGGGAGACCAGUUUCAAGCAGUUUUGAUC CAAUCAAGUUUCCUGAGGAUCAGUUCAAUGUUGCGCUU GAUCAAGUCUUCGAAAGCAUUGAGAACAGUCAGGCACU AGUGGACCAGUCAAACAAAAUUCUAAACAGUGCAGAAA AAGGAAACACUGGUUUCAUUAUCGUAGUAAUUUUGGU UGCUGUUCUUGGUCUAACCAUGAUUUCAGUGAGCAUCA UCAUCAUAAUCAAGAAAACAAGGAAGCCCACAGGAGCA CCUCCAGAGCUGAAUGGUGUCACCAACGGCGGUUUCAU ACCACAUAGUUAG	
gb|KJ627414.1|: 3015-4634 Human metapneumovirus strain hMPV/*Homo sapiens*/PER/CFI0497/2010/B, complete genome	AUGUCUUGGAAAGUGAUGAUUAUCAUUUCGUUACUCAU AACACCUCAGCAUGGACUAAAAGAAAGUUAUUUAGAAG AAUCAUGUAGUACUAUAACUGAAGGAUAUCUCAGUGUU UUAAGAACAGGUUGGUACACCAAUGUCUUUACAUUAGA AGUUGGUGAUGUUGAAAAUCUUACAUGUACUGAUGGA CCUAGCUUAAUCAAAACAGAACUUGACCUAACCAAAAG UGCUUUAAGAGAACUCAAAACAGUUUCUGCUGAUCAGU UAGCGAGAGAAGAACAAAUUGAAAAUCCCAGACAAUCA AGGUUUGUCCUAGGUGCAAUAGCUCUUGGAGUUGCCAC AGCAGCAGCAGUCACAGCAGGCAUUGCAAUAGCCAAAA CUAUAAGGCUUGAGAGUGAAGUGAAUGCAAUCAAAGG UGCUCUCAAAACAACCAAUGAGGCAGUAUCAACACUAG GAAAUGGAGUGCGGGUCCUAGCCACUGCAGUAAGAGAG CUGAAAGAAUUUGUGAGCAAAAACCUGACUAGUGCGAU CAACAAGAACAAGUGUGACAUUGCUGAUUUGAAGAUGG CUGUCAGCUUCAGUCAGUUCAACAGAAGAUUCCUAAAU GUUGUGCGGCAGUUUUCAGACAAUGCAGGGAUAACACC AGCAAUAUCAUUGGACCUGAUGAAUGAUGCUGAGCUGG CCAGAGCUGUAUCAUACAUGCCAACAUCUGCAGGACAG AUAAAACUAAUGUUAGAGAACCGUGCAAUGGUGAGGA GAAAAGGAUUUGGAAUCUUGAUAGGGGUCUACGGAAG CUCUGUGAUUUACAUGGUCCAGCUGCCGAUCUUUGGUG UCAUAAAUACACCUUGUUGGAUAAUCAAGGCAGCUCCC UCUUGUUCAGAAAAAGAUGGAAAUUAUGCUUGCCUCCU AAGAGAGGAUCAAGGGUGGUAUUGUAAAAAUGCAGGA UCCACUGUUUACUACCCAAAUGAAAAAGACUGCGAAAC AAGAGGUGAUCAUGUUUUUUGUGACACAGCAGCAGGGA UCAAUGUUGCUGAGCAAUCAAGAGAAUGCAACAUCAAC AUAUCUACCACCAACUACCCAUGCAAAGUCAGCACAGG AAGACACCCUAUCAGCAUGGUUGCACUAUCACCUCUCG GUGCUUUGGUAGCUUGCUACAAAGGGGUUAGCUGCUCG ACUGGCAGUAAUCAGGUUGGAAUAAUCAAACAACUACC UAAAGGCUGCUCAUACAUAACUAACCAGGACGCAGACA CUGUAACAAUUGACAACACUGUGUAUCAACUAAGCAAA GUUGAGGGUGAACAGCAUGUAAUAAAAGGGAGACCAG UUUCAAGCAGUUUUGAUCCAAUCAGGUUUCCUGAGGAU CAGUUCAAUGUUGCGCUUGAUCAAGUCUUUGAAAGCAU UGAAAACAGUCAAGCACUAGUGGACCAGUCAAACAAAA UUCUGAACAGUGCAGAAAAAGGAAACACUGGU UUCAUUAUUGUAAUAAUUUUGAUUGCUGUUCUUGGGU UAACCAUGAUUUCAGUGAGCAUCAUCAUCAUAAUCAAA AAAACAAGGAAGCCCACAGGGGCACCUCCGGAGCUGAA UGGUGUUACCAACGGCGGUUUCAUACCGCAUAGUUAG	59
gb|KJ723483.1|: 5586-7310 Human respiratory syncytial virus strain RSVA/*Homo sapiens*/USA/84I-215A-01/1984, complete genome	AUGGAGUUGCCAAUCCUCAAAACAAAUGCAAUUACCAC AAUCCUUGCUGCAGUCACACUCUGUUUCGCUUCCAGUC AAAACAUCACUGAAGAAUUUUAUCAAUCAACAUGCAGU GCAGUUAGCAAAGGCUAUCUUAGUGCUCUAAGAACUGG UUGGUAUACUAGUGUUAUAACUAUAGAAUUAAGUAAU AUCAAGGAAAAUAAGUGUAAUGGAACAGAUGCUAAGG UAAAAUUGAUAAAACAAGAAUUAGAUAAAUAUAAAAA UGCUGUAACAGAAUUGCAGUUGCUCAUGCAAAGCACAC CAGCAGCCAACAAUCGAGCCAGAAGAGAACUACCAAGG UUUAUGAAUUAUACACUCAAUAAUACCAAAAAUACCAA UGUAACAUUAAGCAAGAAAAGGAAAAGAAGAUUUCUU GGCUUUUUGUUAGGUGUUGGAUCUGCAAUCGCCAGUGG CAUUGCUGUAUCUAAGGUCCUGCACCUAGAAGGGGAAG	60

TABLE 2-continued

hMPV Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
	UGAACAAAAUCAAAAGUGCUCUACUAUCCACAAACAAG	
	GCUGUAGUCAGCUUAUCAAAUGGAGUUAGUGUCUUAAC	
	CAGCAAAGUGUUAGACCUCAAAAACUAUAUAGAUAAAC	
	AGUUGUUACCUAUUGUGAACAAGCAAAGCUGCAGCAUA	
	UCAAACAUUGAAACUGUGAUAGAGUUCCAACAAAAGAA	
	CAACAGACUACUAGAGAUUACCAGGGAAUUUAGUGUUA	
	AUGCAGGUGUAACUACACCUGUAAGCACUUAUAUGUUA	
	ACUAAUAGUGAAUUAUUAUCAUUAAUCAAUGAUAUGCC	
	UAUAACAAAUGAUCAGAAAAAGUUAAUGUCCAACAAUG	
	UUCAAAUAGUUAGACAGCAAAGUUACUCUAUCAUGUCC	
	AUAAUAAAGGAGGAAGUCUUAGCAUAUGUAGUACAAU	
	UACCACUAUAUGGUGUAAUAGAUACACCCUGUUGGAAA	
	CUGCACACAUCCCCUCUAUGUACAACCAACACAAAGGA	
	AGGGUCCAACAUCUGCUUAACAAGAACCGACAGAGGAU	
	GGUAUUGUGACAAUGCAGGAUCAGUAUCUUUCUUCCCA	
	CAAGCUGAAACAUGUAAAGUUCAAUCGAAUCGGGUAUU	
	UUGUGACACAAUGAACAGUUUAACAUUACCAAGUGAAG	
	UAAAUCUCUGCAACAUUGACAUAUUCAACCCCAAAUAU	
	GAUUGCAAAAUUAUGACUUCAAAAACAGAUGUAAGCAG	
	CUCCGUUAUCACAUCUCUAGGAGCCAUUGUGUCAUGCU	
	AUGGCAAAACUAAAUGUACAGCAUCCAAUAAAAAUCGU	
	GGGAUCAUAAAGACAUUUUCUAACGGGUGUGAUUAUG	
	UAUCAAAUAAGGGGGUGGAUACUGUGUCUGUAGGUAA	
	UACAUUAUAUUAUGUAAAUAAGCAAGAAGGCAAAAGU	
	CUCUAUGUAAAAGGUGAACCAAUAAUAAAUUUCUAUGA	
	CCCAUUAGUGUUCCCCUCUGAUGAAUUUGAUGCAUCAA	
	UAUCUCAAGUCAAUGAGAAGAUUAACCAGAGCCUAGCA	
	UUUAUUCGUAAAUCCGAUGAAUUAUUACAUAAUGUAA	
	AUGCUGGUAAAUCCACCACAAAUAUCAUGAUAACUACU	
	AUAAUUAUAGUGAUUAUAGUAAUAUUGUUAUCAUUAA	
	UUGCAGUUGGACUGCUCCUAUACUGCAAGGCCAGAAGC	
	ACACCAGUCACACUAAGUAAGGAUCAACUGAGUGGUAU	
	AAAUAAUAUUGCAUUUAGUAACUGA	

TABLE 3

hMPV Amino Acid Sequences

Description	Sequence	SEQ ID NO:
gi|122891979|gb|EF051124.1| Human metapneumovirus isolate TN/92-4 fusion protein gene, complete cds	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGW YTNVFTLEVGDVENLTCSDGPSLIKTELDLTKSALRELKTVS ADQLAREEQIENPRQSRFVLGAIALGVAAAAAVTAGVAIAK TIRLESEVTAINNALKKTNEAVSTLGNGVRVLATAVRELKD FVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRA MVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPS CSEKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRG DHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRHPISM VALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQF NVALDQVFENIENSQALVDQSNRILSSAEKGNTGFIIVIILIAV LGSSMILVSIFIIIKKTKKPTGAPPELSGVTNNGFIPHN	5
gb|AY525843.1|: 3065-4684 Human metapneumovirus isolate NL/1/99, complete cds	MSWKVMIIISLLITPQHGLKESYLEESCSTITEGYLSVLRTGW YTNVFTLEVGDVENLTCTDGPSLIKTELDLTKSALRELKTVS ADQLAREEQIENPRQSRFVLGAIALGVATAAAVTAGIAIAKT IRLESEVNAIKGALKQTNEAVSTLGNGVRVLATAVRELKEF VSKNLTSAINRNKCDIADLKMAVSFSQFNRRFLNVVRQFSD NAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRAM VRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCS EKNGNYACLLREDQGWYCKNAGSTVYYPNEKDCETRGDH VFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVA LSPLGALVACYKGVSCSIGSNWVGIIKQLPKGCSYITNQDAD TVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNV ALDQVFESIENSQALVDQSNKILNSAEKGNTGFIIVVILVAVL GLTMISVSIIIIIKKTRKPTGAPPELNGVTNGGFIPHS	6
gb|KJ627414.1|: 3015-4634 Human metapneumovirus	MSWKVMIIISLLITPQHGLKESYLEESCSTITEGYLSVLRTGW YTNVFTLEVGDVENLTCTDGPSLIKTELDLTKSALRELKTVS ADQLAREEQIENPRQSRFVLGAIALGVATAAAVTAGIAIAKT	7

TABLE 3-continued

hMPV Amino Acid Sequences

Description	Sequence	SEQ ID NO:
strain hMPV/*Homo sapiens*/PER/CFI0497/2010/B, complete cds	IRLESEVNAIKGALKTTNEAVSTLGNGVRVLATAVRELKEF VSKNLTSAINKNKCDIADLKMAVSFSQFNRRFLNVVRQFSD NAGITPAISLDLMNDAELARAVSYMPTSAGQIKLMLENRAM VRRKGFGILIGVYGSSVIYMVQLPIFGVINTPCWIIKAAPSCS EKDGNYACLLREDQGWYCKNAGSTVYYPNEKDCETRGDH VFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVA LSPLGALVACYKGVSCSTGSNQVGIIKQLPKGCSYITNQDAD TVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIRFPEDQFNV ALDQVFESIENSQALVDQSNKILNSAEKGNTGFIIVIILIAVLG LTMISVSIIIIIKKTRKPTGAPPELNGVTNGGFIPHS	
gb|KJ723483.1|: 5586-7310 Human respiratory syncytial virus strain RSVA/*Homo sapiens*/USA/84I-215A-01/1984, complete cds	MELPILKTNAITTILAAVTLCFASSQNITEEFYQSTCSAVSKG YLSALRTGWYTSVITIELSNIKENKCNGTDAKVKLIKQELDK YKNAVTELQLLMQSTPAANNRARRELPRFMNYTLNNTKNT NVTLSKKRKRRFLGFLLGVGSAIASGIAVSKVLHLEGEVNKI KSALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQLLPIVN KQSCSISNIETVIEFQQKNNRLLEITREFSVNAGVTTPVSTYM LTNSELLSLINDMPITNDQKKLMSNNVQIVRQQSYSIMSIIKE EVLAYVVQLPLYGVIDTPCWKLHTSPLCTTNTKEGSNICLTR TDRGWYCDNAGSVSFFPQAETCKVQSNRVFCDTMNSLTLP SEVNLCNIDIFNPKYDCKIMTSKTDVSSSVITSLGAIVSCYGK TKCTASNKNRGIIKTFSNGCDYVSNKGVDTVSVGNTLYYVN KQEGKSLYVKGEPIINFYDPLVFPSDEFDASISQVNEKINQSL AFIRKSDELLHNVNAGKSTTNIMITTIIIVIIVILLSLIAVGLLL YCKARSTPVTLSKDQLSGINNIAFSN	8

TABLE 4

hMPV NCBI Accession Numbers (Amino Acid Sequences)

Virus	GenBank Accession
F [Human metapneumovirus] [Human metapneumovirus]	AEK26895.1
fusion glycoprotein [Human metapneumovirus]	ACJ53565.1
fusion glycoprotein [Human metapneumovirus]	ACJ53566.1
fusion glycoprotein [Human metapneumovirus]	ACJ53569.1
fusion protein [Human metapneumovirus]	AEZ52347.1
fusion glycoprotein [Human metapneumovirus]	ACJ53574.1
fusion glycoprotein [Human metapneumovirus]	AHV79473.1
fusion glycoprotein [Human metapneumovirus]	ACJ53570.1
fusion glycoprotein [Human metapneumovirus]	ACJ53567.1
fusion protein [Human metapneumovirus]	AAS22125.1
fusion glycoprotein [Human metapneumovirus]	AHV79795.1
fusion glycoprotein [Human metapneumovirus]	AHV79455.1
fusion glycoprotein [Human metapneumovirus]	ACJ53568.1
fusion protein [Human metapneumovirus]	AAS22109.1
fusion glycoprotein [Human metapneumovirus]	AGU68417.1
fusion glycoprotein [Human metapneumovirus]	AGJ74228.1
fusion glycoprotein [Human metapneumovirus]	ACJ53575.1
fusion protein [Human metapneumovirus]	AAU25820.1
fusion glycoprotein [Human metapneumovirus]	AGU68377.1
fusion glycoprotein [Human metapneumovirus]	AGU68371.1
fusion glycoprotein [Human metapneumovirus]	AGJ74087.1
fusion glycoprotein [Human metapneumovirus]	ACJ53560.1
fusion glycoprotein [Human metapneumovirus]	AHV79858.1
fusion glycoprotein [Human metapneumovirus]	ACJ53577.1
fusion protein [Human metapneumovirus]	AAS22085.1
fusion protein [Human metapneumovirus]	AEZ52348.1
fusion glycoprotein [Human metapneumovirus]	AGJ74044.1
fusion glycoprotein [Human metapneumovirus]	ACJ53563.1
fusion glycoprotein precursor [Human metapneumovirus]	YP_012608.1
fusion glycoprotein [Human metapneumovirus]	AGJ74053.1
fusion protein [Human metapneumovirus]	BAM37562.1
fusion glycoprotein [Human metapneumovirus]	ACJ53561.1
fusion glycoprotein [Human metapneumovirus]	AGU68387.1
fusion [Human metapneumovirus]	AGL74060.1
fusion glycoprotein precursor [Human metapneumovirus]	AAV88364.1
fusion protein [Human metapneumovirus]	AAN52910.1
fusion protein [Human metapneumovirus]	AAN52915.1
fusion protein [Human metapneumovirus]	BAM37564.1
fusion glycoprotein precursor [Human metapneumovirus]	BAH59618.1
fusion protein [Human metapneumovirus]	AAQ90144.1

TABLE 4-continued

hMPV NCBI Accession Numbers (Amino Acid Sequences)

Virus	GenBank Accession
fusion glycoprotein [Human metapneumovirus]	AHV79446.1
fusion protein [Human metapneumovirus]	AEL87260.1
fusion glycoprotein [Human metapneumovirus]	AHV79867.1
fusion protein [Human metapneumovirus]	ABQ66027.2
fusion glycoprotein [Human metapneumovirus]	ACJ53621.1
fusion protein [Human metapneumovirus]	AAN52911.1
fusion glycoprotein [Human metapneumovirus]	AHV79536.1
fusion glycoprotein [Human metapneumovirus]	AGU68411.1
fusion protein [Human metapneumovirus]	AEZ52346.1
fusion protein [Human metapneumovirus]	AAN52913.1
fusion protein [Human metapneumovirus]	AAN52908.1
fusion glycoprotein [Human metapneumovirus]	ACJ53553.1
fusion glycoprotein [Human metapneumovirus]	AIY25727.1
fusion protein [Human metapneumovirus]	ABM67072.1
fusion protein [Human metapneumovirus]	AEZ52361.1
fusion protein [Human metapneumovirus]	AAS22093.1
fusion glycoprotein [Human metapneumovirus]	AGH27049.1
fusion protein [Human metapneumovirus]	AAK62968.2
fusion glycoprotein [Human metapneumovirus]	ACJ53556.1
fusion glycoprotein [Human metapneumovirus]	ACJ53620.1
fusion protein [Human metapneumovirus]	ABQ58820.1
F [Human metapneumovirus] [Human metapneumovirus]	AEK26886.1
fusion glycoprotein [Human metapneumovirus]	ACJ53619.1
fusion glycoprotein [Human metapneumovirus]	ACJ53555.1
fusion [Human metapneumovirus]	AGL74057.1
fusion protein [Human metapneumovirus]	ABD27850.1
fusion protein [Human metapneumovirus]	AEZ52349.1
fusion protein [Human metapneumovirus]	ABD27848.1
fusion protein [Human metapneumovirus]	ABD27846.1
fusion protein [Human metapneumovirus]	ABQ66021.1
fusion protein [Human metapneumovirus]	AFM57710.1
fusion protein [Human metapneumovirus]	AFM57709.1
fusion protein [Human metapneumovirus]	ABH05968.1
fusion protein [Human metapneumovirus]	AEZ52350.1
fusion protein [Human metapneumovirus]	AFM57712.1
fusion protein [Human metapneumovirus]	AEZ52364.1
fusion protein [Human metapneumovirus]	AAN52912.1
fusion protein [Human metapneumovirus]	AEZ52363.1
fusion [Human metapneumovirus]	AGL74059.1
fusion glycoprotein [Human metapneumovirus]	ACJ53583.1
fusion protein [Human metapneumovirus]	AEZ52356.1
fusion protein [Human metapneumovirus]	AEZ52353.1
fusion glycoprotein [Human metapneumovirus]	ACJ53581.1
fusion glycoprotein [Human metapneumovirus]	ACJ53578.1
fusion protein [Human metapneumovirus]	AAS22117.1
fusion protein [Human metapneumovirus]	BAN75965.1
fusion protein [Human metapneumovirus]	AGF92105.1
fusion protein [Human metapneumovirus]	AAS22077.1
fusion protein [Human metapneumovirus]	AAN52909.1
fusion glycoprotein [Human metapneumovirus]	ACJ53586.1
fusion protein [Human metapneumovirus]	AAQ90145.1
fusion glycoprotein [Human metapneumovirus]	AGT75042.1
fusion [Human metapneumovirus]	AGL74058.1
fusion protein [Human metapneumovirus]	AEL87263.1
fusion glycoprotein [Human metapneumovirus]	AGH27057.1
fusion glycoprotein [Human metapneumovirus]	AHV79491.1
F [Human metapneumovirus] [Human metapneumovirus]	AEK26906.1
fusion glycoprotein [Human metapneumovirus]	ACJ53580.1
fusion protein [Human metapneumovirus]	AEZ52354.1
fusion protein [Human metapneumovirus]	AAN52914.1
G [Human metapneumovirus] [Human metapneumovirus]	AEK26901.1
glycoprotein [Human metapneumovirus]	AFI56738.1
glycoprotein [Human metapneumovirus]	AFI56739.1
glycoprotein [Human metapneumovirus]	AFI56745.1
G protein [Human metapneumovirus]	AAQ62718.1
G protein [Human metapneumovirus]	AAQ62719.1
attachment glycoprotein G [Human metapneumovirus]	AGH27104.1
G protein [Human metapneumovirus]	AAQ62729.1
G protein [Human metapneumovirus]	AAQ62728.1
glycoprotein [Human metapneumovirus]	AFI56753.1
glycoprotein [Human metapneumovirus]	AFI56746.1
glycoprotein [Human metapneumovirus]	AFI56750.1
glycoprotein [Human metapneumovirus]	AFI56747.1
G protein [Human metapneumovirus]	AAQ62721.1
glycoprotein [Human metapneumovirus]	AAT46573.1
glycoprotein [Human metapneumovirus]	AFI56748.1

TABLE 4-continued

hMPV NCBI Accession Numbers (Amino Acid Sequences)

Virus	GenBank Accession
glycoprotein [Human metapneumovirus]	AFI56736.1
glycoprotein [Human metapneumovirus]	AFI56749.1
attachment glycoprotein G [Human metapneumovirus]	AGH27131.1
attachment glycoprotein G [Human metapneumovirus]	AHV79558.1
glycoprotein [Human metapneumovirus]	AFI56740.1
glycoprotein [Human metapneumovirus]	AFI56741.1
glycoprotein [Human metapneumovirus]	AFI56744.1
attachment glycoprotein G [Human metapneumovirus]	AHV79790.1
attachment glycoprotein G [Human metapneumovirus]	AGH27122.1
attachment glycoprotein G [Human metapneumovirus]	AHV79763.1
attachment glycoprotein G [Human metapneumovirus]	AGZ48849.1
glycoprotein [Human metapneumovirus]	AFI56743.1
attachment glycoprotein G [Human metapneumovirus]	AHV79450.1
glycoprotein [Human metapneumovirus]	AFI56751.1
attachment glycoprotein [Human metapneumovirus]	AAS48482.1
attachment glycoprotein G [Human metapneumovirus]	AHV79889.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43050.1
glycoprotein [Human metapneumovirus]	AFI56754.1
attachment glycoprotein G [Human metapneumovirus]	AHV79601.1
glycoprotein [Human metapneumovirus]	AFI56752.1
attachment glycoprotein G [Human metapneumovirus]	AHV79871.1
G protein [Human metapneumovirus]	AEZ68099.1
attachment glycoprotein G [Human metapneumovirus]	AHV79817.1
attachment glycoprotein G [Human metapneumovirus]	AHV79943.1
attachment glycoprotein G [Human metapneumovirus]	BAN75968.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43045.1
attachment glycoprotein G [Human metapneumovirus]	AHV79628.1
attachment glycoprotein [Human metapneumovirus]	AFK49783.1
G protein [Human metapneumovirus]	AAQ62723.1
attachment glycoprotein [Human metapneumovirus]	ABD27839.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43046.1
G protein [Human metapneumovirus]	AAQ62717.1
glycoprotein [Human metapneumovirus]	AFI56742.1
attachment protein [Human metapneumovirus]	ABQ44522.1
glycoprotein [Human metapneumovirus]	AFI56735.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43065.1
G protein [Human metapneumovirus]	AAQ62724.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43075.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43062.1
glycoprotein [Human metapneumovirus]	AAT46579.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43064.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43054.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43042.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43078.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43067.1
G protein [Human metapneumovirus]	AAQ62722.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43063.1
glycoprotein [Human metapneumovirus]	AAT46571.1
glycoprotein [Human metapneumovirus]	AAT46578.1
attachment glycoprotein G [Human metapneumovirus]	AGJ74232.1
glycoprotein [Human metapneumovirus]	AAT46580.1
glycoprotein [Human metapneumovirus]	AAT46574.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43061.1
attachment glycoprotein [Human metapneumovirus]	AFK49791.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43047.1
glycoprotein [Human metapneumovirus]	ABC26386.1
attachment glycoprotein [Human metapneumovirus]	AAS48466.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43048.1
attachment glycoprotein G [Human metapneumovirus]	AGH27140.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43049.1
attachment glycoprotein G [Human metapneumovirus]	AGJ74082.1
attachment glycoprotein G [Human metapneumovirus]	AHV79442.1
attachment glycoprotein G [Human metapneumovirus]	AGJ74091.1
attachment glycoprotein G [Human metapneumovirus]	AHV79477.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43056.1
attachment protein [Human metapneumovirus]	ABQ44523.1
attachment glycoprotein G [Human metapneumovirus]	BAH59622.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43070.1
glycoprotein [Human metapneumovirus]	AAT46585.1
attachment glycoprotein G [Human metapneumovirus]	AGU68409.1
attachment glycoprotein G [Human metapneumovirus]	AGJ74223.1
attachment glycoprotein [Human metapneumovirus]	AAS22129.1
attachment glycoprotein G [Human metapneumovirus]	AGJ74048.1
G protein [Human metapneumovirus]	AAQ62725.1
glycoprotein [Human metapneumovirus]	ABC26384.1
attachment protein [Human metapneumovirus]	ABQ44525.1

TABLE 4-continued

hMPV NCBI Accession Numbers (Amino Acid Sequences)

Virus	GenBank Accession
attachment glycoprotein G [Human metapneumovirus]	YP_012612.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43071.1
attachment glycoprotein G [Human metapneumovirus]	AGJ74162.1
attachment glycoprotein G [Human metapneumovirus]	AGH27095.1
attachment glycoprotein G [Human metapneumovirus]	AHV79531.1
G protein [Human metapneumovirus]	AAQ62726.1
attachment glycoprotein [Human metapneumovirus]	AAS48465.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43058.1
P [Human metapneumovirus] [Human metapneumovirus]	AEK26894.1
phosphoprotein [Human metapneumovirus]	AHV79631.1
phosphoprotein [Human metapneumovirus]	AHV79901.1
phosphoprotein [Human metapneumovirus]	AHV79570.1
phosphoprotein [Human metapneumovirus]	AGJ74076.1
phosphoprotein [Human metapneumovirus]	AAS22123.1
phosphoprotein [Human metapneumovirus]	ABB16895.1
phosphoprotein [Human metapneumovirus]	AHV79579.1
phosphoprotein [Human metapneumovirus]	AGJ74244.1
phosphoprotein [Human metapneumovirus]	AHV79856.1
phosphoprotein [Human metapneumovirus]	ACJ70113.1
phosphoprotein [Human metapneumovirus]	AGZ48843.1
phosphoprotein [Human metapneumovirus]	AHV79498.1
phosphoprotein [Human metapneumovirus]	AHV79480.1
phosphoprotein [Human metapneumovirus]	ABQ43382.1
phosphoprotein [Human metapneumovirus]	AAS22107.1
phosphoprotein [Human metapneumovirus]	ABB16898.1
phosphoprotein [Human metapneumovirus]	AGH27134.1
phosphoprotein [Human metapneumovirus]	ABB16899.1
phosphoprotein [Human metapneumovirus]	AGH27098.1
phosphoprotein [Human metapneumovirus]	AAN52866.1
phosphoprotein [Human metapneumovirus]	AAS22083.1
phosphoprotein [Human metapneumovirus]	YP_012606.1
phosphoprotein [Human metapneumovirus]	AHV79973.1
phosphoprotein [Human metapneumovirus]	AHV79462.1
phosphoprotein [Human metapneumovirus]	AGJ74042.1
phosphoprotein [Human metapneumovirus]	AAV88362.1
P [Human metapneumovirus] [Human metapneumovirus]	AIL23591.1
phosphoprotein [Human metapneumovirus]	AHV79453.1
phosphoprotein [Human metapneumovirus]	AGJ74261.1
phosphoprotein [Human metapneumovirus]	AGH27116.1
phosphoprotein [Human metapneumovirus]	ABB16444.1
phosphoprotein [Human metapneumovirus]	ABB16445.1
phosphoprotein [Human metapneumovirus]	AHV79507.1
phosphoprotein [Human metapneumovirus]	BAH59616.1
phosphoprotein [Human metapneumovirus]	ABB16443.1
phosphoprotein [Human metapneumovirus]	ABQ43388.1
phosphoprotein [Human metapneumovirus]	ABQ43389.1
phosphoprotein [Human metapneumovirus]	ABQ43395.1
phosphoprotein [Human metapneumovirus]	ABQ43385.1
phosphoprotein [Human metapneumovirus]	AAP84042.1
phosphoprotein [Human metapneumovirus]	AAN52868.1
phosphoprotein [Human metapneumovirus]	AAP84041.1
phosphoprotein [Human metapneumovirus]	AGH27080.1
phosphoprotein [Human metapneumovirus]	ABQ43387.1
phosphoprotein [Human metapneumovirus]	AAS22099.1
phosphoprotein [Human metapneumovirus]	ABB16896.1
phosphoprotein [Human metapneumovirus]	AGJ74094.1
phosphoprotein [Human metapneumovirus]	AEZ68089.1
phosphoprotein [Human metapneumovirus]	ABK97002.1
phosphoprotein [Human metapneumovirus]	AAP13486.1
phosphoprotein [Human metapneumovirus]	AHV79444.1
phosphoprotein [Human metapneumovirus]	AHV79865.1
phosphoprotein [Human metapneumovirus]	AGJ74226.1
phosphoprotein [Human metapneumovirus]	ABQ43383.1
phosphoprotein [Human metapneumovirus]	AAN52863.1
phosphoprotein [Human metapneumovirus]	AHV79775.1
phosphoprotein [Human metapneumovirus]	AEZ68094.1
phosphoprotein [Human metapneumovirus]	AHV79883.1
phosphoprotein [Human metapneumovirus]	AEZ68092.1
phosphoprotein [Human metapneumovirus]	ABQ43390.1
phosphoprotein [Human metapneumovirus]	ABQ43386.1
phosphoprotein [Human metapneumovirus]	ABQ43391.1
phosphoprotein [Human metapneumovirus]	ACS16062.1
phosphoprotein [Human metapneumovirus]	AEZ68090.1
phosphoprotein [Human metapneumovirus]	AAK62967.1
phosphoprotein [Human metapneumovirus]	AEZ68093.1
phosphoprotein [Human metapneumovirus]	AEZ68088.1

TABLE 4-continued

hMPV NCBI Accession Numbers (Amino Acid Sequences)

Virus	GenBank Accession
phosphoprotein [Human metapneumovirus]	ABQ43392.1
phosphoprotein [Human metapneumovirus]	ABQ43393.1
phosphoprotein [Human metapneumovirus]	ABQ43384.1
phosphoprotein [Human metapneumovirus]	ABQ43394.1
phosphoprotein [Human metapneumovirus]	ABK96999.1
phosphoprotein [Human metapneumovirus]	AHV79489.1
phosphoprotein [Human metapneumovirus]	AGJ74235.1
phosphoprotein [Human metapneumovirus]	AAS22075.1
phosphoprotein [Human metapneumovirus]	AAS22115.1
phosphoprotein [Human metapneumovirus]	AII17601.1
phosphoprotein [Human metapneumovirus]	ABK97000.1
phosphoprotein [Human metapneumovirus]	AHV79561.1
phosphoprotein [Human metapneumovirus]	AGT75040.1
phosphoprotein [Human metapneumovirus]	AAN52864.1
phosphoprotein [Human metapneumovirus]	ABK97001.1
phosphoprotein [Human metapneumovirus]	AGT74979.1
phosphoprotein [Human metapneumovirus]	AHV79955.1
phosphoprotein [Human metapneumovirus]	AGH27055.1
phosphoprotein [Human metapneumovirus]	AAV88361.1
phosphoprotein [Human metapneumovirus]	ABQ43397.1
phosphoprotein [Human metapneumovirus]	AGJ74173.1
P [Human metapneumovirus] [Human metapneumovirus]	AEK26904.1
phosphoprotein [Human metapneumovirus]	ACJ70104.1
phosphoprotein [Human metapneumovirus]	ABK97003.1
phosphoprotein [Human metapneumovirus]	AGT74955.1
phosphoprotein [Human metapneumovirus]	AAN52856.1
phosphoprotein [Human metapneumovirus]	AAN52862.1
phosphoprotein [Human metapneumovirus]	AGJ74138.1
phosphoprotein [Human metapneumovirus]	AHV79613.1
phosphoprotein [Human metapneumovirus]	AGJ74060.1
phosphoprotein [Human metapneumovirus]	AAQ67684.1
phosphoprotein [Human metapneumovirus]	AEA02278.1
N [Human metapneumovirus] [Human metapneumovirus]	AEK26899.1
nucleoprotein [Human metapneumovirus]	ACS16061.1
nucleoprotein [Human metapneumovirus]	AAS88425.1
nucleoprotein [Human metapneumovirus]	YP_012605.1
nucleoprotein [Human metapneumovirus]	AHV79882.1
nucleoprotein [Human metapneumovirus]	AHV79774.1
nucleocapsid protein [Human metapneumovirus]	AAN52886.1
nucleoprotein [Human metapneumovirus]	AAS22082.1
nucleoprotein [Human metapneumovirus]	AHV79864.1
nucleoprotein [Human metapneumovirus]	AHV79828.1
nucleoprotein [Human metapneumovirus]	AGJ74084.1
nucleocapsid protein [Human metapneumovirus]	AAN52888.1
N [Human metapneumovirus] [Human metapneumovirus]	AIL23590.1
nucleoprotein [Human metapneumovirus]	AAK62966.1
nucleoprotein [Human metapneumovirus]	AHV79972.1
nucleoprotein [Human metapneumovirus]	AHV79470.1
nucleoprotein [Human metapneumovirus]	AHV79452.1
nucleoprotein [Human metapneumovirus]	AGJ74243.1
nucleoprotein [Human metapneumovirus]	AHV79533.1
nucleoprotein [Human metapneumovirus]	AGJ74181.1
nucleoprotein [Human metapneumovirus]	AHV79497.1
nucleoprotein [Human metapneumovirus]	AHV79702.1
nucleoprotein [Human metapneumovirus]	AHV79648.1
nucleoprotein [Human metapneumovirus]	AHV79435.1
putative nucleoprotein [Human metapneumovirus]	AGJ74260.1
nucleocapsid protein [Human metapneumovirus]	AAN52887.1
nucleoprotein [Human metapneumovirus]	AGU68386.1
nucleocapsid protein [Human metapneumovirus]	AAN52899.1
nucleoprotein [Human metapneumovirus]	AAR17673.1
nucleocapsid protein [Human metapneumovirus]	AAN52898.1
nucleoprotein [Human metapneumovirus]	AEA02277.1
nucleoprotein [Human metapneumovirus]	AHV79612.1
nucleoprotein [Human metapneumovirus]	AGU68416.1
nucleoprotein [Human metapneumovirus]	AGU68408.1
nucleoprotein [Human metapneumovirus]	AGU68370.1
nucleoprotein [Human metapneumovirus]	AAQ67683.1
nucleoprotein [Human metapneumovirus]	AGJ74137.1
nucleoprotein [Human metapneumovirus]	AGU68344.1
nucleocapsid protein [Human metapneumovirus]	ABK96997.1
nucleoprotein [Human metapneumovirus]	AGU68413.1
nucleocapsid protein [Human metapneumovirus]	AAN52891.1
nucleoprotein [Human metapneumovirus]	AGU68360.1
nucleoprotein [Human metapneumovirus]	AGU68353.1
nucleocapsid protein [Human metapneumovirus]	ABK96996.1

TABLE 4-continued

hMPV NCBI Accession Numbers (Amino Acid Sequences)

Virus	GenBank Accession
nucleoprotein [Human metapneumovirus]	AAR17666.1
N [Human metapneumovirus] [Human metapneumovirus]	AEK26903.1
nucleoprotein [Human metapneumovirus]	AGT75039.1
nucleoprotein [Human metapneumovirus]	AGU68410.1
nucleoprotein [Human metapneumovirus]	AAS22074.1
nucleoprotein [Human metapneumovirus]	AHV79560.1
nucleoprotein [Human metapneumovirus]	AGT74978.1
nucleoprotein [Human metapneumovirus]	AGJ74128.1
nucleoprotein [Human metapneumovirus]	AAR17663.1
nucleoprotein [Human metapneumovirus]	AAR17662.1
nucleoprotein [Human metapneumovirus]	AAR17664.1
nucleoprotein [Human metapneumovirus]	AAR17657.1
nucleoprotein [Human metapneumovirus]	AAR17659.1
nucleoprotein [Human metapneumovirus]	AAR17661.1
nucleoprotein [Human metapneumovirus]	AGU68352.1
nucleoprotein [Human metapneumovirus]	AGU68373.1
nucleoprotein [Human metapneumovirus]	AGU68376.1
nucleoprotein [Human metapneumovirus]	AGU68342.1
nucleoprotein [Human metapneumovirus]	AGU68365.1
nucleoprotein [Human metapneumovirus]	AGU68363.1
nucleoprotein [Human metapneumovirus]	AGU68398.1
nucleoprotein [Human metapneumovirus]	AGU68348.1
nucleoprotein [Human metapneumovirus]	AGU68354.1
nucleoprotein [Human metapneumovirus]	AGU68391.1
nucleoprotein [Human metapneumovirus]	AGU68389.1
nucleoprotein [Human metapneumovirus]	AGU68399.1
nucleoprotein [Human metapneumovirus]	AGU68337.1
nucleoprotein [Human metapneumovirus]	AAR17660.1
nucleoprotein [Human metapneumovirus]	AAR17667.1
nucleoprotein [Human metapneumovirus]	AGU68402.1
nucleoprotein [Avian metapneumovirus type C]	CDN30025.1
nucleoprotein [Avian metapneumovirus]	AGZ87947.1
Nucleoprotein [Avian metapneumovirus type C]	CAL25113.1
nucleocapsid protein [Avian metapneumovirus]	ABO42286.1
nucleocapsid protein [Avian metapneumovirus]	AAK38430.1
nucleocapsid protein [Avian metapneumovirus]	AAK54155.1
nucleocapsid protein [Avian metapneumovirus]	AAK38426.1
nucleocapsid protein [Avian metapneumovirus]	AAK38425.1
nucleocapsid protein [Avian metapneumovirus]	AAK38424.1
nucleocapsid protein [Avian metapneumovirus]	AAF05909.1
nucleocapsid protein [Avian metapneumovirus]	AAK38435.1
nucleocapsid protein [Avian metapneumovirus]	AAK38428.1
nucleoprotein [Human metapneumovirus]	AAR17669.1
nucleocapsid protein [Avian metapneumovirus]	AAK38429.1
nucleocapsid protein [Avian metapneumovirus]	AAK38427.1
nucleocapsid protein [Avian metapneumovirus]	AAK38423.1
nucleocapsid protein [Avian metapneumovirus]	AAK38434.1
nucleoprotein [Human metapneumovirus]	AGU68338.1
nucleoprotein [Avian metapneumovirus]	YP_443837.1
nucleoprotein [Human metapneumovirus]	AGU68384.1
nucleocapsid protein [Avian metapneumovirus]	AAK38431.1
nucleoprotein [Human metapneumovirus]	AGU68405.1
nucleoprotein [Human metapneumovirus]	AGU68382.1
nucleoprotein [Human metapneumovirus]	AGU68395.1
nucleocapsid [Human metapneumovirus]	AAL35389.3
nucleoprotein [Human metapneumovirus]	AEZ68064.1

TABLE 5

PIV3 Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
>gb|KJ672601.1|: 4990-6609 Human parainfluenza virus 3 strain HPIV3/*Homo sapiens*/PER/FLA4815/2008[fusion glycoprotein F0]	ATGCCAATTTCAATACTGTTAATTATTACAACCATGATC ATGGCATCACACTGCCAAATAGACATCACAAAACTACA GCATGTAGGTGTATTGGTCAACAGTCCCAAAGGGATGA AGATATCACAAAACTTCGAAACAAGATATCTAATCCTGA GTCTCATACCAAAAATAGAAGATTCTAACTCTTGTGGTG ACCAACAGATCAAGCAATACAAGAGGTTATTGGATAGA CTGATCATTCCTTTATATGATGGACTAAGATTACAGAAG GATGTGATAGTGACTAATCAAGAATCCAATGAAAACAC TGATCCCAGAACAGAACGATTCTTTGGAGGGGTAATTGG	9

TABLE 5-continued

PIV3 Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
	AACTATTGCTCTAGGAGTAGCAACCTCAGCACAAATTAC	
	AGCAGCAGTTGCTCTGGTTGAAGCCAAGCAGGCAAGAT	
	CAGACATTGAAAAACTCAAGGAAGCAATCAGGGACACA	
	AATAAAGCAGTGCAGTCAGTTCAGAGCTCTGTAGGAAA	
	TTTGATAGTAGCAATTAAATCAGTCCAGGATTATGTCAA	
	CAAAGAAATCGTGCCATCGATTGCGAGACTAGGTTGTG	
	AAGCAGCAGGACTTCAGTTAGGGATTGCATTAACACAG	
	CATTACTCAGAATTAACAAATATATTTGGTGATAACATA	
	GGATCGTTACAAGAAAAAGGAATAAAATTACAAGGTAT	
	AGCATCATTATACCGTACAAATATCACAGAAATATTCAC	
	AACATCAACAGTTGACAAATATGATATTTATGATCTATT	
	ATTTACAGAATCAATAAAGGTGAGAGTTATAGATGTTGA	
	TTTGAATGATTACTCAATAACCCTCCAAGTCAGACTCCC	
	TTTATTGACCAGACTGCTGAACACTCAAATCTACAAAGT	
	AGATTCCATATCATACAATATCCAAAATAGAGAATGGTA	
	TATCCCTCTTCCCAGCCATATCATGACGAAAGGGGCATT	
	TCTAGGTGGAGCAGATGTCAAAGAATGCATAGAAGCAT	
	TCAGCAGTTATATATGCCCTTCTGATCCAGGATTTGTACT	
	AAACCATGAAATGGAGAGCTGTCTATCAGGAAACATAT	
	CCCAATGTCCAAGAACCACAGTCACATCAGACATAGTTC	
	CTAGGTATGCATTTGTCAATGGAGGAGTGGTTGCGAATT	
	GTATAACAACTACATGTACATGCAATGGTATCGGTAATA	
	GAATCAACCAACCACCTGATCAAGGAGTCAAAATTATA	
	ACACATAAAGAATGTAATACAATAGGTATCAACGGAAT	
	GCTATTCAACACAAACAAAGAAGGAACTCTTGCATTCTA	
	CACACCAGACGACATAACATTAAACAATTCTGTTGCACT	
	TGATCCGATTGACATATCAATCGAGCTCAACAAGGCCAA	
	ATCAGATCTTGAGGAATCAAAAGAATGGATAAGAAGGT	
	CAAATCAAAAGCTAGATTCTATTGGAAGTTGGCATCAAT	
	CTAGCACTACAATCATAGTTATTTTGATAATGATGATTA	
	TATTGTTTATAATTAATATAACAATAATTACAATTGCAA	
	TTAAGTATTACAGAATTCAAAAGAGAAATCGAGTGGAT	
	CAAAATGATAAGCCGTATGTATTAACAAACAAG	
gi|612507167|gb|AHX22430.1| hemagglutinin-neuraminidase [Human parainfluenza virus 3]	ATGGAATACTGGAAGCACACCAACCACGGAAAGGATGC	10
	TGGTAATGAGCTGGAGACATCCACAGCCACTCATGGCA	
	ACAAGCTCACCAACAAGATAACATATATATTGTGGACG	
	ATAACCCTGGTGTTATTATCAATAGTCTTCATCATAGTG	
	CTAACTAATTCCATCAAAAGTGAAAAGGCCCGCGAATC	
	ATTGCTACAAGACATAAATAATGAGTTTATGGAAGTTAC	
	AGAAAAGATCCAAGTGGCATCGGATAATACTAATGATC	
	TAATACAGTCAGGAGTGAATACAAGGCTTCTTACAATTC	
	AGAGTCATGTCCAGAATTATATACCAATATCATTGACAC	
	AACAAATATCGGATCTTAGGAAATTCATTAGTGAAATTA	
	CAATTAGAAATGATAATCAAGAAGTGCCACCACAAAGA	
	ATAACACATGATGTGGGTATAAAACCTTTAAATCCAGAT	
	GATTTCTGGAGATGCACGTCTGGTCTTCCATCTTTGATG	
	AAAACTCCAAAAATAAGATTAATGCCGGGACCAGGATT	
	ATTAGCTATGCCAACGACTGTTGATGGCTGTGTCAGAAC	
	CCCGTCCTTAGTGATAAATGATCTGATTTATGCTTACAC	
	CTCAAATCTAATTACTCGAGGTTGCCAGGATATAGGGAA	
	ATCATATCAAGTATTACAGATAGGGATAATAACTGTAAA	
	CTCAGACTTGGTACCTGACTTAAATCCTAGGATCTCTCA	
	TACCTTCAACATAAATGACAATAGAAAGTCATGTTCTCT	
	AGCACTCCTAAATACAGATGTATATCAACTGTGTTCAAC	
	CCCAAAAGTTGATGAAAGATCAGATTATGCATCATCAG	
	GCATAGAAGATATTGTACTTGATATTGTCAATTATGATG	
	GCTCAATCTCGACAACAAGATTTAAGAATAATAATATAA	
	GTTTTGATCAACCATATGCGGCATTATACCCATCTGTTG	
	GACCAGGGATATACTACAAAGGCAAAATAATATTTCTC	
	GGGTATGGAGGTCTTGAACATCCAATAAATGAGAATGC	
	AATCTGCAACACAACTGGGTGTCCTGGGAAAACACAGA	
	GAGACTGTAATCAAGCATCTCATAGTCCATGGTTTTCAG	
	ATAGAAGGATGGTCAACTCTATAATTGTTGTTGACAAGG	
	GCTTGAACTCAGTTCCAAAATTGAAGGTATGGACGATAT	
	CTATGAGACAAAATTACTGGGGGTCAGAAGGAAGATTA	
	CTTCTACTAGGTAACAAGATCTACATATACACAAGATCT	
	ACAAGTTGGCACAGCAAGTTACAATTAGGAATAATTGA	
	CATTACTGACTACAGTGATATAAGGATAAAATGGACAT	
	GGCATAATGTGCTATCAAGACCAGGAAACAATGAATGT	
	CCATGGGGACATTCATGTCCGGATGGATGTATAACGGG	
	AGTATATACCGATGCATATCCACTCAATCCCACAGGAAG	
	CATTGTATCATCTGTCATATTGGACTCACAAAAATCGAG	
	AGTCAACCCAGTCATAACTTACTCAACAGCAACCGAAA	
	GGGTAAACGAGCTGGCTATCCGAAACAAAACACTCTCA	

TABLE 5-continued

PIV3 Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
	GCTGGGTACACAACAACAAGCTGCATTACACACTATAA CAAAGGGTATTGTTTTCATATAGTAGAAATAAATCATAA AAGCTTAAACACATTTCAACCCATGTTGTTCAAAACAGA GATTCCAAAAAGCTGCAGT	
HPIV3_HN_Codon Optimized	ATGGAATACTGGAAGCACACCAACCACGGCAAGGACGC CGGCAACGAGCTGGAAACCAGCACAGCCACACACGGCA ACAAGCTGACCAACAAGATCACCTACATCCTGTGGACC ATCACCCTGGTGCTGCTGAGCATCGTGTTCATCATCGTG CTGACCAATAGCATCAAGAGCGAGAAGGCCAGAGAGAG CCTGCTGCAGGACATCAACAACGAGTTCATGGAAGTGA CCGAGAAGATCCAGGTGGCCAGCGACAACACCAACGAC CTGATCCAGAGCGGCGTGAACACCCGGCTGCTGACCATC CAGAGCCACGTGCAGAACTACATCCCCATCAGCCTGACC CAGCAGATCAGCGACCTGCGGAAGTTCATCAGCGAGAT CACCATCCGGAACGACAACCAGGAAGTGCCCCCCCAGA GAATCACCCACGACGTGGGCATCAAGCCCCTGAACCCC GACGATTTCTGGCGGTGTACAAGCGGCCTGCCCAGCCTG ATGAAGACCCCCAAGATCCGGCTGATGCCTGGCCCTGG ACTGCTGGCCATGCCTACCACAGTGGATGGCTGTGTGCG GACCCCCAGCCTCGTGATCAACGATCTGATCTACGCCTA CACCAGCAACCTGATCACCCGGGGCTGCCAGGATATCG GCAAGAGCTACCAGGTGCTGCAGATCGGCATCATCACC GTGAACTCCGACCTGGTGCCCGACCTGAACCCTCGGATC AGCCACACCTTCAACATCAACGACAACAGAAAGAGCTG CAGCCTGGCTCTGCTGAACACCGACGTGTACCAGCTGTG CAGCACCCCCAAGGTGGACGAGAGAAGCGACTACGCCA GCAGCGGCATCGAGGATATCGTGCTGGACATCGTGAAC TACGACGGCAGCATCAGCACCACCCGGTTCAAGAACAA CAACATCAGCTTCGACCAGCCCTACGCCGCCCTGTACCC TTCTGTGGGCCCTGGCATCTACTACAAGGGCAAGATCAT CTTCCTGGGCTACGGCGGCCTGGAACACCCCATCAACGA GAACGCCATCTGCAACACCACCGGCTGCCCTGGCAAGA CCCAGAGAGACTGCAATCAGGCCAGCCACAGCCCCTGG TTCAGCGACCGCAGAATGGTCAACTCTATCATCGTGGTG GACAAGGGCCTGAACAGCGTGCCCAAGCTGAAAGTGTG GACAATCAGCATGCGCCAGAACTACTGGGGCAGCGAGG GCAGACTTCTGCTGCTGGGAAACAAGATCTACATCTACA CCCGGTCCACCAGCTGGCACAGCAAACTGCAGCTGGGA ATCATCGACATCACCGACTACAGCGACATCCGGATCAA GTGGACCTGGCACAACGTGCTGAGCAGACCCGGCAACA ATGAGTGCCCTTGGGGCCACAGCTGCCCCGATGGATGTA TCACCGGCGTGTACACCGACGCCTACCCCCTGAATCCTA CCGGCTCCATCGTGTCCAGCGTGATCCTGGACAGCCAGA AAAGCAGAGTGAACCCCGTGATCACATACAGCACCGCC ACCGAGAGAGTGAACGAACTGGCCATCAGAAACAAGAC CCTGAGCGCCGGCTACACCACCACAAGCTGCATCACAC ACTACAACAAGGGCTACTGCTTCCACATCGTGGAAATCA ACCACAAGTCCCTGAACACCTTCCAGCCCATGCTGTTCA AGACCGAGATCCCCAAGAGCTGCTCC	11
HPIV3_F_Codon Optimized	ATGCCCATCAGCATCCTGCTGATCATCACCACAATGATC ATGGCCAGCCACTGCCAGATCGACATCACCAAGCTGCA GCACGTGGGCGTGCTCGTGAACAGCCCCAAGGGCATGA AGATCAGCCAGAACTTCGAGACACGCTACCTGATCCTGA GCCTGATCCCCAAGATCGAGGACAGCAACAGCTGCGGC GACCAGCAGATCAAGCAGTACAAGCGGCTGCTGGACAG ACTGATCATCCCCCTGTACGACGGCCTGCGGCTGCAGAA AGACGTGATCGTGACCAACCAGGAAAGCAACGAGAACA CCGACCCCCGGACCGAGAGATTCTTCGGCGGCGTGATCG GCACAATCGCCCTGGGAGTGGCCACAAGCGCCCAGATT ACAGCCGCTGTGGCCCTGGTGGAAGCCAAGCAGGCCAG AAGCGACATCGAGAAGCTGAAAGAGGCCATCCGGGACA CCAACAAGGCCGTGCAGAGCGTGCAGTCCAGCGTGGGC AATCTGATCGTGGCCATCAAGTCCGTGCAGGACTACGTG AACAAAGAAATCGTGCCCTCTATCGCCCGGCTGGGCTGT GAAGCTGCCGGACTGCAGCTGGGCATTGCCCTGACACA GCACTACAGCGAGCTGACCAACATCTTCGGCGACAACA TCGGCAGCCTGCAGGAAAAGGGCATTAAGCTGCAGGGA ATCGCCAGCCTGTACCGCACCAACATCACCGAGATCTTC ACCACCAGCACCGTGGATAAGTACGACATCTACGACCT GCTGTTCACCGAGAGCATCAAAGTGCGCGTGATCGACGT GGACCTGAACGACTACAGCATCACCCTGCAAGTGCGGC TGCCCCTGCTGACCAGACTGCTGAACACCCAGATCTACA AGGTGGACAGCATCTCCTACAACATCCAGAACCGCGAG	12

TABLE 5-continued

PIV3 Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
	TGGTACATCCCTCTGCCCAGCCACATTATGACCAAGGGC GCCTTTCTGGGCGGAGCCGACGTGAAAGAGTGCATCGA GGCCTTCAGCAGCTACATCTGCCCCAGCGACCCTGGCTT CGTGCTGAACCACGAGATGGAAAGCTGCCTGAGCGGCA ACATCAGCCAGTGCCCCAGAACCACCGTGACCTCCGAC ATCGTGCCCAGATACGCCTTCGTGAATGGCGGCGTGGTG GCCAACTGCATCACCACCACCTGTACCTGCAACGGCATC GGCAACCGGATCAACCAGCCTCCCGATCAGGGCGTGAA GATTATCACCCACAAAGAGTGTAACACCATCGGCATCA ACGGCATGCTGTTCAATACCAACAAAGAGGGCACCCTG GCCTTCTACACCCCCGACGATATCACCCTGAACAACTCC GTGGCTCTGGACCCCATCGACATCTCCATCGAGCTGAAC AAGGCCAAGAGCGACCTGGAAGAGTCCAAAGAGTGGAT CCGGCGGAGCAACCAGAAGCTGGACTCTATCGGCAGCT GGCACCAGAGCAGCACCACCATCATCGTGATCCTGATTA TGATGATTATCCTGTTCATCATCAACATTACCATCATCAC TATCGCCATTAAGTACTACCGGATCCAGAAACGGAACC GGGTGGACCAGAATGACAAGCCCTACGTGCTGACAAAC AAG	
	PIV3 mRNA Sequences	
>gb|KJ672601.1|: 4990-6609 Human parainfluenza virus 3 strain HPIV3/*Homo sapiens*/PER/FLA4815/ 2008[fusion glycoprotein F0]	AUGCCAAUUUCAAUACUGUUAAUUAUUACAACCAUGA UCAUGGCAUCACACUGCCAAAUAGACAUCACAAAACU ACAGCAUGUAGGUGUAUUGGUCAACAGUCCCAAAGGG AUGAAGAUAUCACAAAACUUCGAAACAAGAUAUCUAA UCCUGAGUCUCAUACCAAAAAUAGAAGAUUCUAACUC UUGUGGUGACCAACAGAUCAAGCAAUACAAGAGGUUA UUGGAUAGACUGAUCAUUCCUUUAUAUGAUGGACUAA GAUUACAGAAGGAUGUGAUAGUGACUAAUCAAGAAUC CAAUGAAAACACUGAUCCCAGAACAGAACGAUUCUUU GGAGGGGUAAUUGGAACUAUUGCUCUAGGAGUAGCAA CCUCAGCACAAAUUACAGCAGCAGUUGCUCUGGUUGA AGCCAAGCAGGCAAGAUCAGACAUUGAAAAACUCAAG GAAGCAAUCAGGGACACAAAUAAAGCAGUGCAGUCAG UUCAGAGCUCUGUAGGAAAUUUGAUAGUAGCAAUUAA AUCAGUCCAGGAUUAUGUCAACAAAGAAAUCGUGCCA UCGAUUGCGAGACUAGGUUGUGAAGCAGCAGGACUUC AGUUAGGGAUUGCAUUAACACAGCAUUACUCAGAAUU AACAAAUAUAUUUGGUGAUAACAUAGGAUCGUUACAA GAAAAAGGAAUAAAAUUACAAGGUAUAGCAUCAUUAU ACCGUACAAAUAUCACAGAAAUAUUCACAACAUCAAC AGUUGACAAAUAUGAUAUUUAUGAUCUAUUAUUUACA GAAUCAAUAAAGGUGAGAGUUAUAGAUGUUGAUUUGA AUGAUUACUCAAUAACCCUCCAAGUCAGACUCCCUUU AUUGACCAGACUGCUGAACACUCAAAUCUACAAAGUA GAUUCCAUAUCAUACAAUAUCCAAAAUAGAGAAUGGU AUAUCCCUCUUCCCAGCCAUAUCAUGACGAAAGGGGC AUUUCUAGGUGGAGCAGAUGUCAAAGAAUGCAUAGAA GCAUUCAGCAGUUAUAUAUGCCCUUCUGAUCCAGGAU UUGUACUAAACCAUGAAAUGGAGAGCUGUCUAUCAGG AAACAUAUCCCAAUGUCCAAGAACCACAGUCACAUCA GACAUAGUUCCUAGGUAUGCAUUUGUCAAUGGAGGAG UGGUUGCGAAUUGUAUAACAACUACAUGUACAUGCAA UGGUAUCGGUAAUAGAAUCAACCAACCACCUGAUCAA GGAGUCAAAAUUAUAACACAUAAAGAAUGUAAUACAA UAGGUAUCAACGGAAUGCUAUUCAACACAAACAAAGA AGGAACUCUUGCAUUCUACACACCAGACGACAUAACA UUAAACAAUUCUGUUGCACUUGAUCCGAUUGACAUAU CAAUCGAGCUCAACAAGGCCAAAUCAGAUCUUGAGGA AUCAAAAGAAUGGAUAAGAAGGUCAAAUCAAAAGCUA GAUUCUAUUGGAAGUUGGCAUCAAUCUAGCACUACAA UCAUAGUUAUUUUGAUAAUGAUGAUUAUAUUGUUUAU AAUUAAUAUAACAAUAAUUACAAUUGCAAUUAAGUAU UACAGAAUUCAAAAGAGAAAUCGAGUGGAUCAAAAUG AUAAGCCGUAUGUAUUAACAAACAAG	61
gi|612507167|gb|AHX22430.1| hemagglutinin-neuraminidase [Human parainfluenza virus 3]	AUGGAAUACUGGAAGCACACCAACCACGGAAAGGAUG CUGGUAAUGAGCUGGAGACAUCCACAGCCACUCAUGG CAACAAGCUCACCAACAAGAUAACAUAUAUAUUGUGG ACGAUAACCCUGGUGUUAUUAUCAAUAGUCUUCAUCA UAGUGCUAACUAAUUCCAUCAAAAGUGAAAAGGCCCG CGAAUCAUUGCUACAAGACAUAAAUAAUGAGUUUAUG GAAGUUACAGAAAAGAUCCAAGUGGCAUCGGAUAAUA CUAAUGAUCUAAUACAGUCAGGAGUGAAUACAAGGCU	62

TABLE 5-continued

PIV3 Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
	UCUUACAAUUCAGAGUCAUGUCCAGAAUUAUAUACCA	
	AUAUCAUUGACACAACAAAUAUCGGAUCUUAGGAAAU	
	UCAUUAGUGAAAUUACAAUUAGAAAUGAUAAUCAAGA	
	AGUGCCACCACAAAGAAUAACACAUGAUGUGGGUAUA	
	AAACCUUUAAAUCCAGAUGAUUUCUGGAGAUGCACGU	
	CUGGUCUUCCAUCUUUGAUGAAAACUCCAAAAAUAAG	
	AUUAAUGCCGGGACCAGGAUUAUUAGCUAUGCCAACG	
	ACUGUUGAUGGCUGUGUCAGAACCCCGUCCUUAGUGA	
	UAAAUGAUCUGAUUUAUGCUUACACCUCAAAUCUAAU	
	UACUCGAGGUUGCCAGGAUAUAGGGAAAUCAUAUCAA	
	GUAUUACAGAUAGGGAUAAUAACUGUAAACUCAGACU	
	UGGUACCUGACUUAAAUCCUAGGAUCUCUCAUACCUU	
	CAACAUAAAUGACAAUAGAAAGUCAUGUUCUCUAGCA	
	CUCCUAAAUACAGAUGUAUAUCAACUGUGUUCAACCC	
	CAAAAGUUGAUGAAAGAUCAGAUUAUGCAUCAUCAGG	
	CAUAGAAGAUAUUGUACUUGAUAUUGUCAAUUAUGAU	
	GGCUCAAUCUCGACAACAAGAUUUAAGAAUAAUAAUA	
	UAAGUUUUGAUCAACCAUAUGCGGCAUUAUACCCAUC	
	UGUUGGACCAGGGAUAUACUACAAAGGCAAAAUAAUA	
	UUUCUCGGGUAUGGAGGUCUUGAACAUCCAAUAAAUG	
	AGAAUGCAAUCUGCAACACAACUGGGUGUCCUGGGAA	
	AACACAGAGAGACUGUAAUCAAGCAUCUCAUAGUCCA	
	UGGUUUUCAGAUAGAAGGAUGGUCAACUCUAUAAUUG	
	UUGUUGACAAGGGCUUGAACUCAGUUCCAAAAUUGAA	
	GGUAUGGACGAUAUCUAUGAGACAAAAUUACUGGGGG	
	UCAGAAGGAAGAUUACUUCUACUAGGUAACAAGAUCU	
	ACAUAUACACAAGAUCUACAAGUUGGCACAGCAAGUU	
	ACAAUUAGGAAUAAUUGACAUUACUGACUACAGUGAU	
	AUAAGGAUAAAAUGGACAUGGCAUAAUGUGCUAUCAA	
	GACCAGGAAACAAUGAAUGUCCAUGGGGACAUUCAUG	
	UCCGGAUGGAUGUAUAACGGGAGUAUAUACCGAUGCA	
	UAUCCACUCAAUCCCACAGGAAGCAUUGUAUCAUCUG	
	UCAUAUUGGACUCACAAAAAUCGAGAGUCAACCCAGU	
	CAUAACUUACUCAACAGCAACCGAAAGGGUAAACGAG	
	CUGGCUAUCCGAAACAAAACACUCUCAGCUGGGUACA	
	CAACAACAAGCUGCAUUACACACUAUAACAAAGGGUA	
	UUGUUUUCAUAUAGUAGAAAUAAAUCAUAAAAGCUUA	
	AACACAUUUCAACCCAUGUUGUUCAAAACAGAGAUUC	
	CAAAAAGCUGCAGU	
HPIV3_HN_Codon Optimized	AUGGAAUACUGGAAGCACACCAACCACGGCAAGGACG	63
	CCGGCAACGAGCUGGAAACCAGCACAGCCACACACGGC	
	AACAAGCUGACCAACAAGAUCACCUACAUCCUGUGGA	
	CCAUCACCCUGGUGCUGCUGAGCAUCGUGUUCAUCAUC	
	GUGCUGACCAAUAGCAUCAAGAGCGAGAAGGCCAGAG	
	AGAGCCUGCUGCAGGACAUCAACAACGAGUUCAUGGA	
	AGUGACCGAGAAGAUCCAGGUGGCCAGCGACAACACC	
	AACGACCUGAUCCAGAGCGGCGUGAACACCCGGCUGCU	
	GACCAUCCAGAGCCACGUGCAGAACUACAUCCCCAUCA	
	GCCUGACCCAGCAGAUCAGCGACCUGCGGAAGUUCAUC	
	AGCGAGAUCACCAUCCGGAACGACAACCAGGAAGUGC	
	CCCCCCAGAGAAUCACCCACGACGUGGGCAUCAAGCCC	
	CUGAACCCCGACGAUUUCUGGCGGUGUACAAGCGGCC	
	UGCCCAGCCUGAUGAAGACCCCCAAGAUCCGGCUGAUG	
	CCUGGCCCUGGACUGCUGGCCAUGCCUACCACAGUGGA	
	UGGCUGUGUGCGGACCCCCAGCCUCGUGAUCAACGAUC	
	UGAUCUACGCCUACACCAGCAACCUGAUCACCCGGGGC	
	UGCCAGGAUAUCGGCAAGAGCUACCAGGUGCUGCAGA	
	UCGGCAUCAUCACCGUGAACUCCGACCUGGUGCCCGAC	
	CUGAACCCUCGGAUCAGCCACACCUUCAACAUCAACGA	
	CAACAGAAAGAGCUGCAGCCUGGCUCUGCUGAACACC	
	GACGUGUACCAGCUGUGCAGCACCCCCAAGGUGGACG	
	AGAGAAGCGACUACGCCAGCAGCGGCAUCGAGGAUAU	
	CGUGCUGGACAUCGUGAACUACGACGGCAGCAUCAGC	
	ACCACCCGGUUCAAGAACAACAACAUCAGCUUCGACCA	
	GCCCUACGCCGCCCUGUACCCUUCUGUGGGCCCUGGCA	
	UCUACUACAAGGGCAAGAUCAUCUUCCUGGGCUACGG	
	CGGCCUGGAACACCCCAUCAACGAGAACGCCAUCUGCA	
	ACACCACCGGCUGCCCUGGCAAGACCCAGAGAGACUGC	
	AAUCAGGCCAGCCACAGCCCCUGGUUCAGCGACCGCAG	
	AAUGGUCAACUCUAUCAUCGUGGUGGACAAGGGCCUG	
	AACAGCGUGCCCAAGCUGAAAGUGUGGACAAUCAGCA	
	UGCGCCAGAACUACUGGGGCAGCGAGGGCAGACUUCU	
	GCUGCUGGGAAACAAGAUCUACAUCUACACCCGGUCC	
	ACCAGCUGGCACAGCAAACUGCAGCUGGGAAUCAUCG	

TABLE 5-continued

PIV3 Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
	ACAUCACCGACUACAGCGACAUCCGGAUCAAGUGGACC UGGCACAACGUGCUGAGCAGACCCGGCAACAAUGAGU GCCCUUGGGGCCACAGCUGCCCCGAUGGAUGUAUCACC GGCGUGUACACCGACGCCUACCCCCUGAAUCCUACCGG CUCCAUCGUGUCCAGCGUGAUCCUGGACAGCCAGAAA AGCAGAGUGAACCCCGUGAUCACAUACAGCACCGCCAC CGAGAGAGUGAACGAACUGGCCAUCAGAAACAAGACC CUGAGCGCCGGCUACACCACCACAAGCUGCAUCACACA CUACAACAAGGGCUACUGCUUCCACAUCGUGGAAAUC AACCACAAGUCCCUGAACACCUUCCAGCCCAUGCUGUU CAAGACCGAGAUCCCCAAGAGCUGCUCC	
HPIV3_F_Codon Optimized mRNA sequence	AUGCCCAUCAGCAUCCUGCUGAUCAUCACCACAAUGAU CAUGGCCAGCCACUGCCAGAUCGACAUCACCAAGCUGC AGCACGUGGGCGUGCUCGUGAACAGCCCCAAGGGCAU GAAGAUCAGCCAGAACUUCGAGACACGCUACCUGAUC CUGAGCCUGAUCCCCAAGAUCGAGGACAGCAACAGCU GCGGCGACCAGCAGAUCAAGCAGUACAAGCGGCUGCU GGACAGACUGAUCAUCCCCCUGUACGACGGCCUGCGGC UGCAGAAAGACGUGAUCGUGACCAACCAGGAAAGCAA CGAGAACACCGACCCCCGGACCGAGAGAUUCUUCGGCG GCGUGAUCGGCACAAUCGCCCUGGGAGUGGCCACAAG CGCCCAGAUUACAGCCGCUGUGGCCCUGGUGGAAGCCA AGCAGGCCAGAAGCGACAUCGAGAAGCUGAAAGAGGC CAUCCGGGACACCAACAAGGCCGUGCAGAGCGUGCAG UCCAGCGUGGGCAAUCUGAUCGUGGCCAUCAAGUCCG UGCAGGACUACGUGAACAAAGAAAUCGUGCCCUCUAU CGCCCGGCUGGGCUGUGAAGCUGCCGGACUGCAGCUG GGCAUUGCCCUGACACAGCACUACAGCGAGCUGACCAA CAUCUUCGGCGACAACAUCGGCAGCCUGCAGGAAAAG GGCAUUAAGCUGCAGGGAAUCGCCAGCCUGUACCGCA CCAACAUCACCGAGAUCUUCACCACCAGCACCGUGGAU AAGUACGACAUCUACGACCUGCUGUUCACCGAGAGCA UCAAAGUGCGCGUGAUCGACGUGGACCUGAACGACUA CAGCAUCACCCUGCAAGUGCGGCUGCCCCUGCUGACCA GACUGCUGAACACCCAGAUCUACAAGGUGGACAGCAU CUCCUACAACAUCCAGAACCGCGAGUGGUACAUCCCUC UGCCCAGCCACAUUAUGACCAAGGGCGCCUUUCUGGGC GGAGCCGACGUGAAAGAGUGCAUCGAGGCCUUCAGCA GCUACAUCUGCCCCAGCGACCCUGGCUUCGUGCUGAAC CACGAGAUGGAAAGCUGCCUGAGCGGCAACAUCAGCC AGUGCCCCAGAACCACCGUGACCUCCGACAUCGUGCCC AGAUACGCCUUCGUGAAUGGCGGCGUGGUGGCCAACU GCAUCACCACCACCUGUACCUGCAACGGCAUCGGCAAC CGGAUCAACCAGCCUCCCGAUCAGGGCGUGAAGAUUA UCACCCACAAAGAGUGUAACACCAUCGGCAUCAACGGC AUGCUGUUCAAUACCAACAAAGAGGGCACCCUGGCCU UCUACACCCCCGACGAUAUCACCCUGAACAACUCCGUG GCUCUGGACCCCAUCGACAUCUCCAUCGAGCUGAACAA GGCCAAGAGCGACCUGGAAGAGUCCAAAGAGUGGAUC CGGCGGAGCAACCAGAAGCUGGACUCUAUCGGCAGCU GGCACCAGAGCAGCACCACCAUCAUCGUGAUCCUGAUU AUGAUGAUUAUCCUGUUCAUCAUCAACAUUACCAUCA UCACUAUCGCCAUUAAGUACUACCGGAUCCAGAAACG GAACCGGGUGGACCAGAAUGACAAGCCCUACGUGCUG ACAAACAAG	64

TABLE 6

PIV3 Amino Acid Sequences

Description	Sequence	SEQ ID NO:
>gi|612507166|gb| AHX22429.1| fusion glycoprotein F0 [Human parainfluenza virus 3]	MPISILLIITTMIMASHCQIDITKLQHVGVLVNSPKGMKISQ NFETRYLILSLIPKIEDSNSCGDQQIKQYKRLLDRLIIPLYDG LRLQKDVIVTNQESNENTDPRTERFFGGVIGTIALGVATSA QITAAVALVEAKQARSDIEKLKEAIRDTNKAVQSVQSSVG NLIVAIKSVQDYVNKEIVPSIARLGCEAAGLQLGIALTQHYS ELTNIFGDNIGSLQEKGIKLQGIASLYRTNITEIFTTSTVDKY DIYDLLFTESIKVRVIDVDLNDYSITLQVRLPLLTRLLNTQIY	13

TABLE 6-continued

PIV3 Amino Acid Sequences

Description	Sequence	SEQ ID NO:
	KVDSISYNIQNREWYIPLPSHIMTKGAFLGGADVKECIEAFS SYICPSDPGFVLNHEMESCLSGNISQCPRTTVTSDIVPRYAF VNGGVVANCITTTCTCNGIGNRINQPPDQGVKIITHKECNTI GINGMLFNTNKEGTLAFYTPDDITLNNSVALDPIDISIELNK AKSDLEESKEWIRRSNQKLDSIGSWHQSSTTIIVILIMMIILFI INITIITIAIKYYRIQKRNRVDQNDKPYVLTNK	
gi|612507167|gb|AHX22430.1| hemagglutinin- neuraminidase [Human parainfluenza virus 3]	MEYWKHTNHGKDAGNELETSTATHGNKLTNKITYILWTIT LVLLSIVFIIVLTNSIKSEKARESLLQDINNEFMEVTEKIQVA SDNTNDLIQSGVNTRLLTIQSHVQNYIPISLTQQISDLRKFIS EITIRNDNQEVPPQRITHDVGIKPLNPDDFWRCTSGLPSLMK TPKIRLMPGPGLLAMPTTVDGCVRTPSLVINDLIYAYTSNLI TRGCQDIGKSYQVLQIGIITVNSDLVPDLNPRISHTFNINDN RKSCSLALLNTDVYQLCSTPKVDERSDYASSGIEDIVLDIV NYDGSISTTRFKNNNISFDQPYAALYPSVGPGIYYKGKIIFL GYGGLEHPINENAICNTTGCPGKTQRDCNQASHSPWFSDR RMVNSIIVVDKGLNSVPKLKVWTISMRQNYWGSEGRLLLL GNKIYIYTRSTSWHSKLQLGIIDITDYSDIRIKWTWHNVLSR PGNNECPWGHSCPDGCITGVYTDAYPLNPTGSIVSSVILDS QKSRVNPVITYSTATERVNELAIRNKTLSAGYTTTSCITHY NKGYCFHIVEINHKSLNTFQPMLFKTEIPKSCS	14

TABLE 7

PIV3 NCBI Accession Numbers (Nucleic Acid and Amino Acid Sequences)

Description	GenBank Accession
Fusion glycoprotein F0 [Human parainfluenza virus 3] HPIV3/*Homo sapiens*/PER/FLA4815/2008	KJ672601.1|: 4990-6609 AHX22429 (Fusion protein)
hemagglutinin-neuraminidase [Human parainfluenza virus 3] HPIV3/*Homo sapiens*/PER/FLA4815/2008	KJ672601.1|: 6724-8442 AHX22430 (HN protein)
Recombinant PIV3/PIV1 virus fusion glycoprotein (F) and hemagglutinin (HN) genes, complete cds; and RNA dependent RNA polymerase (L) gene, partial cds.	AF016281 AAC23947 (hemagglutinin)
Recombinant PIV3/PIV1 virus fusion glycoprotein (F) and hemagglutinin (HN) genes, complete cds; and RNA dependent RNA polymerase (L) gene, partial cds.	AF016281 AAC23947 (fusion protein)
hemagglutinin-neuraminidase [Human parainfluenza virus 3]	BAO32044.1
hemagglutinin-neuraminidase [Human parainfluenza virus 3]	BAO32051.1
C protein [Human parainfluenza virus 3]	NP_599251.1
C protein [Human parainfluenza virus 3]	ABZ85670.1
C protein [Human parainfluenza virus 3]	AGT75164.1
C protein [Human parainfluenza virus 3]	AAB48686.1
C protein [Human parainfluenza virus 3]	AHX22115.1
C protein [Human parainfluenza virus 3]	AGW51066.1
C protein [Human parainfluenza virus 3]	AGW51162.1
C protein [Human parainfluenza virus 3]	AGT75252.1
C protein [Human parainfluenza virus 3]	AGT75188.1
C protein [Human parainfluenza virus 3]	AGW51218.1
C protein [Human parainfluenza virus 3]	AGW51074.1
C protein [Human parainfluenza virus 3]	AGT75323.1
C protein [Human parainfluenza virus 3]	AGT75307.1
C protein [Human parainfluenza virus 3]	AHX22131.1
C protein [Human parainfluenza virus 3]	AGW51243.1
C protein [Human parainfluenza virus 3]	AGT75180.1
C protein [Human parainfluenza virus 3]	AGT75212.1
C protein [Human parainfluenza virus 3]	AGW51186.1
C protein [Human parainfluenza virus 3]	AHX22075.1
C protein [Human parainfluenza virus 3]	AHX22163.1
C protein [Human parainfluenza virus 3]	AGT75196.1
C protein [Human parainfluenza virus 3]	AHX22491.1
C protein [Human parainfluenza virus 3]	AHX22139.1
C protein [Human parainfluenza virus 3]	AGW51138.1
C protein [Human parainfluenza virus 3]	AGW51114.1
C protein [Human parainfluenza virus 3]	AGT75220.1
C protein [Human parainfluenza virus 3]	AHX22251.1
RecName: Full = Protein C; AltName: Full = VP18 protein	P06165.1

TABLE 7-continued

PIV3 NCBI Accession Numbers (Nucleic Acid and Amino Acid Sequences)

Description	GenBank Accession
C protein [Human parainfluenza virus 3]	AHX22187.1
C protein [Human parainfluenza virus 3]	AGT75228.1
C protein [Human parainfluenza virus 3]	AHX22179.1
C protein [Human parainfluenza virus 3]	AHX22427.1
C protein [Human parainfluenza virus 3]	AGW51210.1
nonstructural protein C [Human parainfluenza virus 3]	BAA00922.1
C protein [Human parainfluenza virus 3]	AHX22315.1
C protein [Human parainfluenza virus 3]	AGW51259.1
C protein [Human parainfluenza virus 3]	AHX22435.1
C protein [Human parainfluenza virus 3]	AHX22123.1
C protein [Human parainfluenza virus 3]	AHX22299.1
C protein [Human parainfluenza virus 3]	AGW51267.1
unnamed protein product [Human parainfluenza virus 3]	CAA28430.1
C protein [Human parainfluenza virus 3]	AGW51178.1
C protein [Human parainfluenza virus 3]	AHX22411.1
RecName: Full = Protein C	P06164.1
phosphoprotein [Human parainfluenza virus 3]	NP_067149.1
phosphoprotein [Human parainfluenza virus 3]	AAB48685.1
phosphoprotein [Human parainfluenza virus 3]	AHX22498.1
phosphoprotein [Human parainfluenza virus 3]	AHX22490.1
phosphoprotein [Human parainfluenza virus 3]	AGT75259.1
phosphoprotein [Human parainfluenza virus 3]	AGW51137.1
phosphoprotein [Human parainfluenza virus 3]	AGW51145.1
phosphoprotein [Human parainfluenza virus 3]	AGT75298.1
phosphoprotein [Human parainfluenza virus 3]	AGW51113.1
phosphoprotein [Human parainfluenza virus 3]	AGT75203.1
phosphoprotein [Human parainfluenza virus 3]	AGT75163.1
phosphoprotein [Human parainfluenza virus 3]	AHX22506.1
phosphoprotein [Human parainfluenza virus 3]	AGW51129.1
phosphoprotein [Human parainfluenza virus 3]	AHX22194.1
phosphoprotein [Human parainfluenza virus 3]	AGT75211.1
phosphoprotein [Human parainfluenza virus 3]	AHX22258.1
phosphoprotein [Human parainfluenza virus 3]	AGW51121.1
phosphoprotein [Human parainfluenza virus 3]	AGT75282.1
phosphoprotein [Human parainfluenza virus 3]	AHX22146.1
phosphoprotein [Human parainfluenza virus 3]	AHX22138.1
phosphoprotein [Human parainfluenza virus 3]	AHX22322.1
phosphoprotein [Human parainfluenza virus 3]	AHX22370.1
phosphoprotein [Human parainfluenza virus 3]	AHX22098.1
phosphoprotein [Human parainfluenza virus 3]	AHX22130.1
phosphoprotein [Human parainfluenza virus 3]	AHX22418.1
phosphoprotein [Human parainfluenza virus 3]	AHX22114.1
phosphoprotein [Human parainfluenza virus 3]	AHX22410.1
phosphoprotein [Human parainfluenza virus 3]	AGT75306.1
phosphoprotein [Human parainfluenza virus 3]	AHX22170.1
phosphoprotein [Human parainfluenza virus 3]	AHX22266.1
phosphoprotein [Human parainfluenza virus 3]	AHX22090.1
phosphoprotein [Human parainfluenza virus 3]	AGT75195.1
phosphoprotein [Human parainfluenza virus 3]	AHX22226.1
phosphoprotein [Human parainfluenza virus 3]	AHX22178.1
phosphoprotein [Human parainfluenza virus 3]	AHX22122.1
phosphoprotein [Human parainfluenza virus 3]	AHX22186.1
phosphoprotein [Human parainfluenza virus 3]	AHX22066.1
phosphoprotein [Human parainfluenza virus 3]	AHX22522.1
phosphoprotein [Human parainfluenza virus 3]	AGW51225.1
phosphoprotein [Human parainfluenza virus 3]	BAN29032.1
phosphoprotein [Human parainfluenza virus 3]	ABZ85669.1
phosphoprotein [Human parainfluenza virus 3]	AHX22426.1
phosphoprotein [Human parainfluenza virus 3]	AHX22058.1
phosphoprotein [Simian Agent 10]	ADR00400.1
phosphoprotein [Human parainfluenza virus 3]	AHX22250.1
phosphoprotein [Human parainfluenza virus 3]	AHX22434.1
phosphoprotein [Human parainfluenza virus 3]	AHX22298.1
phosphoprotein [Human parainfluenza virus 3]	AHX22442.1
phosphoprotein [Human parainfluenza virus 3]	AHX22074.1
phosphoprotein [Human parainfluenza virus 3]	AGW51153.1
phosphoprotein [Human parainfluenza virus 3]	AGW51241.1
phosphoprotein [Human parainfluenza virus 3]	AHX22210.1
phosphoprotein [Human parainfluenza virus 3]	AGW51105.1
phosphoprotein [Human parainfluenza virus 3]	AGT75251.1
phosphoprotein [Human parainfluenza virus 3]	AHX22362.1
phosphoprotein [Human parainfluenza virus 3]	AHX22474.1
phosphoprotein [Human parainfluenza virus 3]	AGW51217.1
phosphoprotein [Human parainfluenza virus 3]	AIG60038.1
phosphoprotein [Human parainfluenza virus 3]	AHX22378.1
phosphoprotein [Human parainfluenza virus 3]	AGW51057.1

TABLE 7-continued

PIV3 NCBI Accession Numbers (Nucleic Acid and Amino Acid Sequences)

Description	GenBank Accession
phosphoprotein [Human parainfluenza virus 3]	AGT75187.1
phosphoprotein [Human parainfluenza virus 3]	AGW51233.1
phosphoprotein [Human parainfluenza virus 3]	AHX22482.1
phosphoprotein [Human parainfluenza virus 3]	AGW51161.1
phosphoprotein [Human parainfluenza virus 3]	AHX22306.1
phosphoprotein [Human parainfluenza virus 3]	AHX22162.1
phosphoprotein [Human parainfluenza virus 3]	ACJ70087.1
phosphoprotein [Human parainfluenza virus 3]	AHX22466.1
phosphoprotein [Human parainfluenza virus 3]	AHX22346.1
phosphoprotein [Human parainfluenza virus 3]	AGW51089.1
phosphoprotein [Human parainfluenza virus 3]	AGW51073.1
phosphoprotein [Human parainfluenza virus 3]	AGW51185.1
phosphoprotein [Human parainfluenza virus 3]	AGW51065.1
phosphoprotein [Human parainfluenza virus 3]	ABY47603.1
phosphoprotein [Human parainfluenza virus 3]	AGW51049.1
phosphoprotein [Human parainfluenza virus 3]	AHX22330.1
phosphoprotein [Human parainfluenza virus 3]	AGW51250.1
phosphoprotein [Human parainfluenza virus 3]	AGT75227.1
phosphoprotein [Human parainfluenza virus 3]	AGW51282.1
phosphoprotein [Human parainfluenza virus 3]	AGW51209.1
phosphoprotein [Human parainfluenza virus 3]	AGW51193.1
phosphoprotein [Human parainfluenza virus 3]	AGT75322.1
phosphoprotein [Human parainfluenza virus 3]	AGT75219.1
phosphoprotein [Human parainfluenza virus 3]	AGW51258.1
phosphoprotein [Human parainfluenza virus 3]	AGW51041.1
phosphoprotein [Human parainfluenza virus 3]	ACD99698.1
phosphoprotein [Human parainfluenza virus 3]	AGW51266.1
phosphoprotein [Human parainfluenza virus 3]	AGT75179.1
phosphoprotein [Human parainfluenza virus 3]	AHX22282.1
phosphoprotein [Human parainfluenza virus 3]	AGW51169.1
phosphoprotein [Human parainfluenza virus 3]	AGW51274.1
phosphoprotein [Human parainfluenza virus 3]	AGW51201.1
phosphoprotein [Human parainfluenza virus 3]	AGW51177.1
RecName: Full = Phosphoprotein; Short = Protein P	P06162.1
P protein [Human parainfluenza virus 3]	AAA66818.1
phosphoprotein [Human parainfluenza virus 3]	AAA46866.1
phosphoprotein [Human parainfluenza virus 3]	BAA00031.1
polymerase-associated nucleocapsid phosphoprotein (version 2) - parainfluenza virus type 3 [Human parainfluenza virus 3]	RRNZP5
phosphoprotein [Human parainfluenza virus 3]	AGT75171.1
phosphoprotein [Human parainfluenza virus 3]	BAA00921.1
D protein [Human parainfluenza virus 3]	NP_599250.1
D protein [Human parainfluenza virus 3]	AHX22377.1
D protein [Human parainfluenza virus 3]	AHX22121.1
D protein [Human parainfluenza virus 3]	AGT75297.1
D protein [Human parainfluenza virus 3]	AGW51136.1
D protein [Human parainfluenza virus 3]	AGW51242.1
D protein [Human parainfluenza virus 3]	AGW51112.1
D protein [Human parainfluenza virus 3]	AHX22497.1
D protein [Human parainfluenza virus 3]	AHX22145.1
D protein [Human parainfluenza virus 3]	AGT75202.1
D protein [Human parainfluenza virus 3]	AHX22385.1
D protein [Human parainfluenza virus 3]	AGW51216.1
D protein [Human parainfluenza virus 3]	AGT75281.1
D protein [Human parainfluenza virus 3]	AGT75194.1
D protein [Human parainfluenza virus 3]	AHX22521.1
D protein [Human parainfluenza virus 3]	AGW51120.1
D protein [Human parainfluenza virus 3]	AGT75313.1
D protein [Human parainfluenza virus 3]	AHX22249.1
D protein [Human parainfluenza virus 3]	AHX22097.1
D protein [Human parainfluenza virus 3]	AGW51144.1
D protein [Human parainfluenza virus 3]	AHX22089.1
D protein [Human parainfluenza virus 3]	AHX22225.1
D protein [Human parainfluenza virus 3]	AHX22137.1
D protein [Human parainfluenza virus 3]	AHX22065.1
D protein [Human parainfluenza virus 3]	AGW51224.1
D protein [Human parainfluenza virus 3]	AGT75210.1
D protein [Human parainfluenza virus 3]	AHX22393.1
D protein [Human parainfluenza virus 3]	AGT75258.1
D protein [Human parainfluenza virus 3]	AHX22345.1
D protein [Human parainfluenza virus 3]	AGT75250.1
D protein [Human parainfluenza virus 3]	AHX22113.1
D protein [Human parainfluenza virus 3]	AGW51232.1
D protein [Human parainfluenza virus 3]	AHX22057.1
D protein [Human parainfluenza virus 3]	AHX22209.1

TABLE 7-continued

PIV3 NCBI Accession Numbers (Nucleic Acid and Amino Acid Sequences)

Description	GenBank Accession
D protein [Human parainfluenza virus 3]	AGW51056.1
D protein [Human parainfluenza virus 3]	AHX22161.1
D protein [Simian Agent 10]	ADR00402.1
D protein [Human parainfluenza virus 3]	AHX22361.1
D protein [Human parainfluenza virus 3]	AGW51281.1
D protein [Human parainfluenza virus 3]	AGW51184.1
D protein [Human parainfluenza virus 3]	AGW51160.1
D protein [Human parainfluenza virus 3]	AHX22465.1
D protein [Human parainfluenza virus 3]	AHX22329.1
D protein [Human parainfluenza virus 3]	AGW51064.1
D protein [Human parainfluenza virus 3]	AGW51040.1
D protein [Human parainfluenza virus 3]	AGT75226.1
D protein [Human parainfluenza virus 3]	AHX22425.1
D protein [Human parainfluenza virus 3]	AHX22305.1
D protein [Human parainfluenza virus 3]	AGW51249.1
D protein [Human parainfluenza virus 3]	AHX22481.1
D protein [Human parainfluenza virus 3]	AHX22281.1
D protein [Human parainfluenza virus 3]	AGW51048.1
D protein [Human parainfluenza virus 3]	AHX22297.1
D protein [Human parainfluenza virus 3]	AGW51088.1
D protein [Human parainfluenza virus 3]	AGT75305.1
D protein [Human parainfluenza virus 3]	AHX22185.1
D protein [Human parainfluenza virus 3]	AGW51104.1
D protein [Human parainfluenza virus 3]	AHX22081.1
D protein [Human parainfluenza virus 3]	AGW51192.1
D protein [Human parainfluenza virus 3]	AHX22489.1
D protein [Human parainfluenza virus 3]	AHX22441.1
D protein [Human parainfluenza virus 3]	AHX22409.1
D protein [Human parainfluenza virus 3]	AHX22369.1
D protein [Human parainfluenza virus 3]	AHX22321.1
D protein [Human parainfluenza virus 3]	AHX22073.1
D protein [Human parainfluenza virus 3]	AGW51152.1
D protein [Human parainfluenza virus 3]	AGW51072.1
D protein [Human parainfluenza virus 3]	AGT75321.1
D protein [Human parainfluenza virus 3]	AHX22257.1
D protein [Human parainfluenza virus 3]	AHX22129.1
D protein [Human parainfluenza virus 3]	AHX22417.1
D protein [Human parainfluenza virus 3]	AGT75218.1
D protein [Human parainfluenza virus 3]	AHX22265.1
D protein [Human parainfluenza virus 3]	AGT75178.1
D protein [Human parainfluenza virus 3]	AHX22433.1
D protein [Human parainfluenza virus 3]	AGW51273.1
D protein [Human parainfluenza virus 3]	AGW51208.1
D protein [Human parainfluenza virus 3]	AGT75170.1
D protein [Human parainfluenza virus 3]	AGT75162.1
D protein [Human parainfluenza virus 3]	AGW51257.1
D protein [Human parainfluenza virus 3]	AGW51200.1
D protein [Human parainfluenza virus 3]	AGW51176.1
D protein [Human parainfluenza virus 3]	AGT75186.1
D protein [Human parainfluenza virus 3]	AGW51265.1
D protein [Human parainfluenza virus 3]	AGW51168.1

TABLE 8

Signal Peptides

Description	Sequence	SEQ ID NO:
HuIgG$_k$ signal peptide	METPAQLLFLLLLWLPDTTG	15
IgE heavy chain epsilon-1 signal peptide	MDWTWILFLVAAATRVHS	16
Japanese encephalitis PRM signal sequence	MLGSNSGQRVVFTILLLLVAPAYS	17
VSVg protein signal sequence	MKCLLYLAFLFIGVNCA	18

TABLE 8-continued

Signal Peptides

Description	Sequence	SEQ ID NO:
Japanese encephalitis JEV signal sequence	MWLVSLAIVTACAGA	19

TABLE 9

hMPV/PIV Cotton Rat Challenge Study Design

Group	n	Test Article	[conc]/μg	Route	Challenge
1	5	Placebo	n/a	IM	hMPV/A2
2	5	hMPV vaccine mRNA	30	IM	hMPV/A2

TABLE 9-continued

hMPV/PIV Cotton Rat Challenge Study Design

Group	n	Test Article	[conc]/μg	Route	Challenge
3	5	hMPV vaccine mRNA	15	IM	hMPV/A2
4	5	hMPV vaccine mRNA	10	IM	hMPV/A2
5	5	hMPV/PIV3 vaccine mRNA (15/15)	30	IM	hMPV/A2
6	5	FI-hMPV	n/a	IM	hMPV/A2
7	5	Placebo	n/a	IM	PIV3
8	5	PIV3 vaccine mRNA	30	IM	PIV3
9	5	PIV3 vaccine mRNA	15	IM	PIV3
10	5	PIV3 vaccine mRNA	10	IM	PIV3
11	5	hMPV/PIV3 vaccine mRNA (15/15)	30	IM	PIV3
12	5	FI-PIV3	n/a	IM	PIV3
	60				

TABLE 10

Betacoronavirus Nucleic Acid Sequence

Strain	Nucleic Acid Sequence	SEQ ID NO:
gb|KJ156934.1|: 21405-25466 Middle East respiratory syndrome coronavirus isolate Riyadh_14_2013, spike protein (nucleotide)	ATGATACACTCAGTGTTTCTACTGATGTTCTTGTTAACACC TACAGAAAGTTACGTTGATGTAGGGCCAGATTCTGTTAAG TCTGCTTGTATTGAGGTTGATATACAACAGACCTTCTTTGA TAAAACTTGGCCTAGGCCAATTGATGTTTCTAAGGCTGAC GGTATTATATACCCTCAAGGCCGTACATATTCTAACATAA CTATCACTTATCAAGGTCTTTTTCCCTATCAGGGAGACCAT GGTGATATGTATGTTTACTCTGCAGGACATGCTACAGGCA CAACTCCACAAAAGTTGTTTGTAGCTAACTATTCTCAGGA CGTCAAACAGTTTGCTAATGGGTTTGTCGTCCGTATAGGA GCAGCTGCCAATTCCACTGGCACTGTTATTATTAGCCCATC TACCAGCGCTACTATACGAAAAATTTACCCTGCTTTTATGC TGGGTTCTTCAGTTGGTAATTTCTCAGATGGTAAAATGGG CCGCTTCTTCAATCATACTCTAGTTCTTTTGCCCGATGGAT GTGGCACTTTACTTAGAGCTTTTTATTGTATTCTAGAGCCT CGCTCTGGAAATCATTGTCCTGCTGGCAATTCCTATACTTC TTTTGCCACTTATCACACTCCTGCAACAGATTGTTCTGATG GCAATTACAATCGTAATGCCAGTCTGAACTCTTTTAAGGA GTATTTTAATTTACGTAACTGCACCTTTATGTACACTTATA ACATTACCGAAGATGAGATTTTAGAGTGGTTTGGCATTAC ACAAACTGCTCAAGGTGTTCACCTCTTCTCATCTCGGTATG TTGATTTGTACGGCGGCAATATGTTTCAATTTGCCACCTTG CCTGTTTATGATACTATTAAGTATTATTCTATCATTCCTCA CAGTATTCGTTCTATCCAAAGTGATAGAAAAGCTTGGGCT GCCTTCTACGTATATAAACTTCAACCGTTAACTTTCCTGTT GGATTTTTCTGTTGATGGTTATATACGCAGAGCTATAGACT GTGGTTTTAATGATTTGTCACAACTCCACTGCTCATATGAA TCCTTCGATGTTGAATCTGGAGTTTATTCAGTTTCGTCTTT CGAAGCAAAACCTTCTGGCTCAGTTGTGGAACAGGCTGAA GGTGTTGAATGTGATTTTTCACCTCTTCTGTCTGGCACACC TCCTCAGGTTTATAATTTCAAGCGTTTGGTTTTTACCAATT GCAATTATAATCTTACCAAATTGCTTTCACTTTTTTCTGTG AATGATTTTACTTGTAGTCAAATATCTCCAGCAGCAATTGC TAGCAACTGTTATTCTTCACTGATTTTGGATTATTTTTCAT ACCCACTTAGTATGAAATCCGATCTCAGTGTTAGTTCTGCT GGTCCAATATCCCAGTTTAATTATAAACAGTCCTTTTCTAA TCCCACATGTTTGATCTTAGCGACTGTTCCTCATAACCTTA CTACTATTACTAAGCCTCTTAAGTACAGCTATATTAACAA GTGCTCTCGTCTTCTTTCTGATGATCGTACTGAAGTACCTC AGTTAGTGAACGCTAATCAATACTCACCCTGTGTATCCATT GTCCCATCCACTGTGTGGGAAGACGGTGATTATTATAGGA AACAACTATCTCCACTTGAAGGTGGTGGCTGGCTTGTTGC TAGTGGCTCAACTGTTGCCATGACTGAGCAATTACAGATG GGCTTTGGTATTACAGTTCAATATGGTACAGACACCAATA GTGTTTGCCCCAAGCTTGAATTTGCTAATGACACAAAAAT TGCCTCTCAATTAGGCAATTGCGTGGAATATTCCCTCTATG GTGTTTCGGGCCGTGGTGTTTTTCAGAATTGCACAGCTGTA GGTGTTCGACAGCAGCGCTTTGTTTATGATGCGTACCAGA ATTTAGTTGGCTATTATTCTGATGATGGCAACTACTACTGT CTGCGTGCTTGTGTTAGTGTTCCTGTTTCTGTCATCTATGA TAAAGAAACTAAAACCCACGCTACTCTATTTGGTAGTGTT GCATGTGAACACATTTCTTCTACCATGTCTCAATACTCCCG TTCTACGCGATCAATGCTTAAACGGCGAGATTCTACATAT GGCCCCCTTCAGACACCTGTTGGTTGTGTCCTAGGACTTGT TAATTCCTCTTTGTTCGTAGAGGACTGCAAGTTGCCTCTCG GTCAATCTCTCTGTGCTCTTCCTGACACACCTAGTACTCTC ACACCTCGCAGTGTGCGCTCTGTGCCAGGTGAAATGCGCT TGGCATCCATTGCTTTTAATCATCCCATTCAGGTTGATCAA CTTAATAGTAGTTATTTTAAATTAAGTATACCCACTAATTT	20

TABLE 10-continued

Betacoronavirus Nucleic Acid Sequence

Strain	Nucleic Acid Sequence	SEQ ID NO:
	TTCCTTTGGTGTGACTCAGGAGTACATTCAGACAACCATTC	
	AGAAAGTTACTGTTGATTGTAAACAGTACGTTTGCAATGG	
	TTTCCAGAAGTGTGAGCAATTACTGCGCGAGTATGGCCAG	
	TTTTGTTCCAAAATAAACCAGGCTCTCCATGGTGCCAATTT	
	ACGCCAGGATGATTCTGTACGTAATTTGTTTGCGAGCGTG	
	AAAAGCTCTCAATCATCTCCTATCATACCAGGTTTTGGAG	
	GTGACTTTAATTTGACACTTCTAGAACCTGTTTCTATATCT	
	ACTGGCAGTCGTAGTGCACGTAGTGCTATTGAGGATTTGC	
	TATTTGACAAAGTCACTATAGCTGATCCTGGTTATATGCA	
	AGGTTACGATGATTGTATGCAGCAAGGTCCAGCATCAGCT	
	CGTGATCTTATTTGTGCTCAATATGTGGCTGGTTATAAAGT	
	ATTACCTCCTCTTATGGATGTTAATATGGAAGCCGCGTATA	
	CTTCATCTTTGCTTGGCAGCATAGCAGGTGTTGGCTGGACT	
	GCTGGCTTATCCTCCTTTGCTGCTATTCCATTTGCACAGAG	
	TATYTTTTATAGGTTAAACGGTGTTGGCATTACTCAACAG	
	GTTCTTTCAGAGAACCAAAAGCTTATTGCCAATAAGTTTA	
	ATCAGGCTCTGGGAGCTATGCAAACAGGCTTCACTACAAC	
	TAATGAAGCTTTTCGGAAGGTTCAGGATGCTGTGAACAAC	
	AATGCACAGGCTCTATCCAAATTAGCTAGCGAGCTATCTA	
	ATACTTTTGGTGCTATTTCCGCCTCTATTGGAGACATCATA	
	CAACGTCTTGATGTTCTCGAACAGGACGCCCAAATAGACA	
	GACTTATTAATGGCCGTTTGACAACACTAAATGCTTTTGTT	
	GCACAGCAGCTTGTTCGTTCCGAATCAGCTGCTCTTTCCGC	
	TCAATTGGCTAAAGATAAAGTCAATGAGTGTGTCAAGGCA	
	CAATCCAAGCGTTCTGGATTTTGCGGTCAAGGCACACATA	
	TAGTGTCCTTTGTTGTAAATGCCCCTAATGGCCTTTACTTT	
	ATGCATGTTGGTTATTACCCTAGCAACCACATTGAGGTTGT	
	TTCTGCTTATGGTCTTTGCGATGCAGCTAACCCTACTAATT	
	GTATAGCCCCTGTTAATGGCTACTTTATTAAAACTAATAAC	
	ACTAGGATTGTTGATGAGTGGTCATATACTGGCTCGTCCTT	
	CTATGCACCTGAGCCCATCACCTCTCTTAATACTAAGTATG	
	TTGCACCACAGGTGACATACCAAAACATTTCTACTAACCT	
	CCCTCCTCCTCTTCTCGGCAATTCCACCGGGATTGACTTCC	
	AAGATGAGTTGGATGAGTTTTTCAAAAATGTTAGCACCAG	
	TATACCTAATTTTGGTTCTCTAACACAGATTAATACTACAT	
	TACTCGATCTTACCTACGAGATGTTGTCTCTTCAACAAGTT	
	GTTAAAGCCCTTAATGAGTCTTACATAGACCTTAAAGAGC	
	TTGGCAATTATACTTATTACAACAAATGGCCGTGGTACAT	
	TTGGCTTGGTTTCATTGCTGGGCTTGTTGCCTTAGCTCTAT	
	GCGTCTTCTTCATACTGTGCTGCACTGGTTGTGGCACAAAC	
	TGTATGGGAAAACTTAAGTGTAATCGTTGTTGTGATAGAT	
	ACGAGGAATACGACCTCGAGCCGCATAAGGTTCATGTTCA	
	CTAA	
MERS S FL SPIKE 2cEMC/2012 (XBaI change(T to G)) (nucleotide)	ATGATACACTCAGTGTTTCTACTGATGTTCTTGTTAACACC	21
	TACAGAAAGTTACGTTGATGTAGGGCCAGATTCTGTTAAG	
	TCTGCTTGTATTGAGGTTGATATACAACAGACTTTCTTTGA	
	TAAAACTTGGCCTAGGCCAATTGATGTTTCTAAGGCTGAC	
	GGTATTATATACCCTCAAGGCCGTACATATTCTAACATAA	
	CTATCACTTATCAAGGTCTTTTTCCCTATCAGGGAGACCAT	
	GGTGATATGTATGTTTACTCTGCAGGACATGCTACAGGCA	
	CAACTCCACAAAAGTTGTTTGTAGCTAACTATTCTCAGGA	
	CGTCAAACAGTTTGCTAATGGGTTTGTCGTCCGTATAGGA	
	GCAGCTGCCAATTCCACTGGCACTGTTATTATTAGCCCATC	
	TACCAGCGCTACTATACGAAAAATTTACCCTGCTTTTATGC	
	TGGGTTCTTCAGTTGGTAATTTCTCAGATGGTAAAATGGG	
	CCGCTTCTTCAATCATACTCTAGTTCTTTTGCCCGATGGAT	
	GTGGCACTTTACTTAGAGCTTTTTATTGTATTCTGGAGCCT	
	CGCTCTGGAAATCATTGTCCTGCTGGCAATTCCTATACTTC	
	TTTTGCCACTTATCACACTCCTGCAACAGATTGTTCTGATG	
	GCAATTACAATCGTAATGCCAGTCTGAACTCTTTTAAGGA	
	GTATTTTAATTTACGTAACTGCACCTTTATGTACACTTATA	
	ACATTACCGAAGATGAGATTTTAGAGTGGTTTGGCATTAC	
	ACAAACTGCTCAAGGTGTTCACCTCTTCTCATCTCGGTATG	
	TTGATTTGTACGGCGGCAATATGTTTCAATTTGCCACCTTG	
	CCTGTTTATGATACTATTAAGTATTATTCTATCATTCCTCA	
	CAGTATTCGTTCTATCCAAAGTGATAGAAAAGCTTGGGCT	
	GCCTTCTACGTATATAAACTTCAACCGTTAACTTTCCTGTT	
	GGATTTTTCTGTTGATGGTTATATACGCAGAGCTATAGACT	
	GTGGTTTTAATGATTTGTCACAACTCCACTGCTCATATGAA	
	TCCTTCGATGTTGAATCTGGAGTTTATTCAGTTTCGTCTTT	
	CGAAGCAAAACCTTCTGGCTCAGTTGTGGAACAGGCTGAA	
	GGTGTTGAATGTGATTTTTCACCTCTTCTGTCTGGCACACC	
	TCCTCAGGTTTATAATTTCAAGCGTTTGGTTTTTACCAATT	
	GCAATTATAATCTTACCAAATTGCTTTCACTTTTTTCTGTG	

TABLE 10-continued

Betacoronavirus Nucleic Acid Sequence

Strain	Nucleic Acid Sequence	SEQ ID NO:
	AATGATTTTACTTGTAGTCAAATATCTCCAGCAGCAATTGC TAGCAACTGTTATTCTTCACTGATTTTGGATTACTTTTCAT ACCCACTTAGTATGAAATCCGATCTCAGTGTTAGTTCTGCT GGTCCAATATCCCAGTTTAATTATAAACAGTCCTTTTCTAA TCCCACATGTTTGATTTTAGCGACTGTTCCTCATAACCTTA CTACTATTACTAAGCCTCTTAAGTACAGCTATATTAACAA GTGCTCTCGTCTTCTTTCTGATGATCGTACTGAAGTACCTC AGTTAGTGAACGCTAATCAATACTCACCCTGTGTATCCATT GTCCCATCCACTGTGTGGGAAGACGGTGATTATTATAGGA AACAACTATCTCCACTTGAAGGTGGTGGCTGGCTTGTTGC TAGTGGCTCAACTGTTGCCATGACTGAGCAATTACAGATG GGCTTTGGTATTACAGTTCAATATGGTACAGACACCAATA GTGTTTGCCCCAAGCTTGAATTTGCTAATGACACAAAAAT TGCCTCTCAATTAGGCAATTGCGTGGAATATTCCCTCTATG GTGTTTCGGGCCGTGGTGTTTTTCAGAATTGCACAGCTGTA GGTGTTCGACAGCAGCGCTTTGTTTATGATGCGTACCAGA ATTTAGTTGGCTATTATTCTGATGATGGCAACTACTACTGT TTGCGTGCTTGTGTTAGTGTTCCTGTTTCTGTCATCTATGAT AAAGAAACTAAAACCCACGCTACTCTATTTGGTAGTGTTG CATGTGAACACATTTCTTCTACCATGTCTCAATACTCCCGT TCTACGCGATCAATGCTTAAACGGCGAGATTCTACATATG GCCCCCTTCAGACACCTGTTGGTTGTGTCCTAGGACTTGTT AATTCCTCTTTGTTCGTAGAGGACTGCAAGTTGCCTCTTGG TCAATCTCTCTGTGCTCTTCCTGACACACCTAGTACTCTCA CACCTCGCAGTGTGCGCTCTGTTCCAGGTGAAATGCGCTT GGCATCCATTGCTTTTAATCATCCTATTCAGGTTGATCAAC TTAATAGTAGTTATTTTAAATTAAGTATACCCACTAATTTT TCCTTTGGTGTGACTCAGGAGTACATTCAGACAACCATTC AGAAAGTTACTGTTGATTGTAAACAGTACGTTTGCAATGG TTTCCAGAAGTGTGAGCAATTACTGCGCGAGTATGGCCAG TTTTGTTCCAAAATAAACCAGGCTCTCCATGGTGCCAATTT ACGCCAGGATGATTCTGTACGTAATTTGTTTGCGAGCGTG AAAAGCTCTCAATCATCTCCTATCATACCAGGTTTTGGAG GTGACTTTAATTTGACACTTCTGGAACCTGTTTCTATATCT ACTGGCAGTCGTAGTGCACGTAGTGCTATTGAGGATTTGC TATTTGACAAAGTCACTATAGCTGATCCTGGTTATATGCA AGGTTACGATGATTGCATGCAGCAAGGTCCAGCATCAGCT CGTGATCTTATTTGTGCTCAATATGTGGCTGGTTACAAAGT ATTACCTCCTCTTATGGATGTTAATATGGAAGCCGCGTATA CTTCATCTTTGCTTGGCAGCATAGCAGGTGTTGGCTGGACT GCTGGCTTATCCTCCTTTGCTGCTATTCCATTTGCACAGAG TATCTTTTATAGGTTAAACGGTGTTGGCATTACTCAACAGG TTCTTTCAGAGAACCAAAAGCTTATTGCCAATAAGTTTAA TCAGGCTCTGGGAGCTATGCAAACAGGCTTCACTACAACT AATGAAGCTTTTCAGAAGGTTCAGGATGCTGTGAACAACA ATGCACAGGCTCTATCCAAATTAGCTAGCGAGCTATCTAA TACTTTTGGTGCTATTTCCGCCTCTATTGGAGACATCATAC AACGTCTTGATGTTCTCGAACAGGACGCCCAAATAGACAG ACTTATTAATGGCCGTTTGACAACACTAAATGCTTTTGTTG CACAGCAGCTTGTTCGTTCCGAATCAGCTGCTCTTTCCGCT CAATTGGCTAAAGATAAAGTCAATGAGTGTGTCAAGGCAC AATCCAAGCGTTCTGGATTTTGCGGTCAAGGCACACATAT AGTGTCCTTTGTTGTAAATGCCCCTAATGGCCTTTACTTCA TGCATGTTGGTTATTACCCTAGCAACCACATTGAGGTTGTT TCTGCTTATGGTCTTTGCGATGCAGCTAACCCTACTAATTG TATAGCCCCTGTTAATGGCTACTTTATTAAAACTAATAACA CTAGGATTGTTGATGAGTGGTCATATACTGGCTCGTCCTTC TATGCACCTGAGCCCATTACCTCCCTTAATACTAAGTATGT TGCACCACAGGTGACATACCAAAACATTTCTACTAACCTC CCTCCTCCTCTTCTCGGCAATTCCACCGGGATTGACTTCCA AGATGAGTTGGATGAGTTTTTCAAAAATGTTAGCACCAGT ATACCTAATTTTGGTTCCCTAACACAGATTAATACTACATT ACTCGATCTTACCTACGAGATGTTGTCTCTTCAACAAGTTG TTAAAGCCCTTAATGAGTCTTACATAGACCTTAAAGAGCT TGGCAATTATACTTATTACAACAAATGGCCGTGGTACATT TGGCTTGGTTTCATTGCTGGGCTTGTTGCCTTAGCTCTATG CGTCTTCTTCATACTGTGCTGCACTGGTTGTGGCACAAACT GTATGGGAAAACTTAAGTGTAATCGTTGTTGTGATAGATA CGAGGAATACGACCTCGAGCCGCATAAGGTTCATGTTCAC TAA	
Novel_MERS_S2_subunit_trimeric vaccine (nucleotide)	ATGATCCACTCCGTGTTCCTCCTCATGTTCCTGTTGACCCC CACTGAGTCAGACTGCAAGCTCCCGCTGGGACAGTCCCTG TGTGCGCTGCCTGACACTCCTAGCACTCTGACCCCACGCTC CGTGCGGTCGGTGCCTGGCGAAATGCGGCTGGCCTCCATC	22

TABLE 10-continued

Betacoronavirus Nucleic Acid Sequence

Strain	Nucleic Acid Sequence	SEQ ID NO:
	GCCTTCAATCACCCAATCCAAGTGGATCAGCTGAATAGCT	
	CGTATTTCAAGCTGTCCATCCCCACGAACTTCTCGTTCGGG	
	GTCACCCAGGAGTACATCCAGACCACAATTCAGAAGGTCA	
	CCGTCGATTGCAAGCAATACGTGTGCAACGGCTTCCAGAA	
	GTGCGAGCAGCTGCTGAGAGAATACGGGCAGTTTTGCAGC	
	AAGATCAACCAGGCGCTGCATGGAGCTAACTTGCGCCAGG	
	ACGACTCCGTGCGCAACCTCTTTGCCTCTGTGAAGTCATCC	
	CAGTCCTCCCCAATCATCCCGGGATTCGGAGGGGACTTCA	
	ACCTGACCCTCCTGGAGCCCGTGTCGATCAGCACCGGTAG	
	CAGATCGGCGCGCTCAGCCATTGAAGATCTTCTGTTCGAC	
	AAGGTCACCATCGCCGATCCGGGCTACATGCAGGGATACG	
	ACGACTGTATGCAGCAGGGACCAGCCTCCGCGAGGGACCT	
	CATCTGCGCGCAATACGTGGCCGGGTACAAAGTGCTGCCT	
	CCTCTGATGGATGTGAACATGGAGGCCGCTTATACTTCGT	
	CCCTGCTCGGCTCTATCGCCGGCGTGGGGTGGACCGCCGG	
	CCTGTCCTCCTTCGCCGCTATCCCCTTTGCACAATCCATTT	
	TCTACCGGCTCAACGGCGTGGGCATTACTCAACAAGTCCT	
	GTCGGAGAACCAGAAGTTGATCGCAAACAAGTTCAATCA	
	GGCCCTGGGGGCCATGCAGACTGGATTCACTACGACTAAC	
	GAAGCGTTCCAGAAGGTCCAGGACGCTGTGAACAACAAC	
	GCCCAGGCGCTCTCAAAGCTGGCCTCCGAACTCAGCAACA	
	CCTTCGGAGCCATCAGCGCATCGATCGGTGACATAATTCA	
	GCGGCTGGACGTGCTGGAGCAGGACGCCCAGATCGACCG	
	CCTCATCAACGGACGGCTGACCACCTTGAATGCCTTCGTG	
	GCACAACAGCTGGTCCGGAGCGAATCAGCGGCACTTTCCG	
	CCCAACTCGCCAAGGACAAAGTCAACGAATGCGTGAAGG	
	CCCAGTCCAAGAGGTCCGGTTTCTGCGGTCAAGGAACCCA	
	TATTGTGTCCTTCGTCGTGAACGCGCCCAACGGTCTGTACT	
	TTATGCACGTCGGCTACTACCCGAGCAATCATATCGAAGT	
	GGTGTCCGCCTACGGCCTGTGCGATGCCGCTAACCCCACT	
	AACTGTATTGCCCCTGTGAACGGATATTTTATTAAGACCA	
	ACAACACCCGCATTGTGGACGAATGGTCATACACCGGTTC	
	GTCCTTCTACGCGCCCGAGCCCATCACTTCACTGAACACC	
	AAATACGTGGCTCCGCAAGTGACCTACCAGAACATCTCCA	
	CCAATTTGCCGCCGCCGCTGCTCGGAAACAGCACCGGAAT	
	TGATTTCCAAGATGAACTGGACGAATTCTTCAAGAACGTG	
	TCCACTTCCATTCCCAACTTCGGAAGCCTGACACAGATCA	
	ACACCACCCTTCTCGACCTGACCTACGAGATGCTGAGCCT	
	TCAACAAGTGGTCAAGGCCCTGAACGAGAGCTACATCGAC	
	CTGAAGGAGCTGGGCAACTATACCTACTACAACAAGTGGC	
	CGGACAAGATTGAGGAGATTCTGTCGAAAATCTACCACAT	
	TGAAAACGAGATCGCCAGAATCAAGAAGCTTATCGGCGA	
	AGCC	
MERS_S0_Full-length Spike protein (nucleotide, codon optimized)	ATGGAAACCCCTGCCCAGCTGCTGTTCCTGCTGCTGCTGTG	23
	GCTGCCTGATACCACCGGCAGCTATGTGGACGTGGGCCCC	
	GATAGCGTGAAGTCCGCCTGTATCGAAGTGGACATCCAGC	
	AGACCTTTTTCGACAAGACCTGGCCCAGACCCATCGACGT	
	GTCCAAGGCCGACGGCATCATCTATCCACAAGGCCGGACC	
	TACAGCAACATCACCATTACCTACCAGGGCCTGTTCCCAT	
	ATCAAGGCGACCACGGCGATATGTACGTGTACTCTGCCGG	
	CCACGCCACCGGCACCACACCCCAGAAACTGTTCGTGGCC	
	AACTACAGCCAGGACGTGAAGCAGTTCGCCAACGGCTTCG	
	TCGTGCGGATTGGCGCCGCTGCCAATAGCACCGGCACAGT	
	GATCATCAGCCCCAGCACCAGCGCCACCATCCGGAAGATC	
	TACCCCGCCTTCATGCTGGGCAGCTCCGTGGGCAATTTCA	
	GCGACGGCAAGATGGGCCGGTTCTTCAACCACACCCTGGT	
	GCTGCTGCCCGATGGCTGTGGCACACTGCTGAGAGCCTTC	
	TACTGCATCCTGGAACCCAGAAGCGGCAACCACTGCCCTG	
	CCGGCAATAGCTACACCAGCTTCGCCACCTACCACACACC	
	CGCCACCGATTGCTCCGACGGCAACTACAACCGGAACGCC	
	AGCCTGAACAGCTTCAAAGAGTACTTCAACCTGCGGAACT	
	GCACCTTCATGTACACCTACAATATCACCGAGGACGAGAT	
	CCTGGAATGGTTCGGCATCACCCAGACCGCCCAGGGCGTG	
	CACCTGTTCAGCAGCAGATACGTGGACCTGTACGGCGGCA	
	ACATGTTCCAGTTTGCCACCCTGCCCGTGTACGACACCATC	
	AAGTACTACAGCATCATCCCCCACAGCATCCGGTCCATCC	
	AGAGCGACAGAAAAGCCTGGGCCGCCTTCTACGTGTACAA	
	GCTGCAGCCCCTGACCTTCCTGCTGGACTTCAGCGTGGAC	
	GGCTACATCAGACGGGCCATCGACTGCGGCTTCAACGACC	
	TGAGCCAGCTGCACTGCTCCTACGAGAGCTTCGACGTGGA	
	AAGCGGCGTGTACAGCGTGTCCAGCTTCGAGGCCAAGCCT	
	AGCGGCAGCGTGGTGGAACAGGCTGAGGGCGTGGAATGC	
	GACTTCAGCCCTCTGCTGAGCGGCACCCCTCCCCAGGTGT	
	ACAACTTCAAGCGGCTGGTGTTCACCAACTGCAATTACAA	

TABLE 10-continued

Betacoronavirus Nucleic Acid Sequence

Strain	Nucleic Acid Sequence	SEQ ID NO:
	CCTGACCAAGCTGCTGAGCCTGTTCTCCGTGAACGACTTC	
	ACCTGTAGCCAGATCAGCCCTGCCGCCATTGCCAGCAACT	
	GCTACAGCAGCCTGATCCTGGACTACTTCAGCTACCCCCT	
	GAGCATGAAGTCCGATCTGAGCGTGTCCTCCGCCGGACCC	
	ATCAGCCAGTTCAACTACAAGCAGAGCTTCAGCAACCCTA	
	CCTGCCTGATTCTGGCCACCGTGCCCCACAATCTGACCAC	
	CATCACCAAGCCCCTGAAGTACAGCTACATCAACAAGTGC	
	AGCAGACTGCTGTCCGACGACCGGACCGAAGTGCCCCAGC	
	TCGTGAACGCCAACCAGTACAGCCCCTGCGTGTCCATCGT	
	GCCCAGCACCGTGTGGGAGGACGGCGACTACTACAGAAA	
	GCAGCTGAGCCCCCTGGAAGGCGGCGGATGGCTGGTGGCT	
	TCTGGAAGCACAGTGGCCATGACCGAGCAGCTGCAGATG	
	GGCTTTGGCATCACCGTGCAGTACGGCACCGACACCAACA	
	GCGTGTGCCCCAAGCTGGAATTCGCCAATGACACCAAGAT	
	CGCCAGCCAGCTGGGAAACTGCGTGGAATACTCCCTGTAT	
	GGCGTGTCCGGACGGGGCGTGTTCCAGAATTGCACAGCAG	
	TGGGAGTGCGGCAGCAGAGATTCGTGTACGATGCCTACCA	
	GAACCTCGTGGGCTACTACAGCGACGACGGCAATTACTAC	
	TGCCTGCGGGCCTGTGTGTCCGTGCCCGTGTCCGTGATCTA	
	CGACAAAGAGACAAAGACCCACGCCACACTGTTCGGCTCC	
	GTGGCCTGCGAGCACATCAGCTCCACCATGAGCCAGTACT	
	CCCGCTCCACCCGGTCCATGCTGAAGCGGAGAGATAGCAC	
	CTACGGCCCCCTGCAGACACCTGTGGGATGTGTGCTGGGC	
	CTCGTGAACAGCTCCCTGTTTGTGGAAGATTGCAAGCTGC	
	CCCTGGGCCAGAGCCTGTGTGCCCTGCCAGATACCCCTAG	
	CACCCTGACCCCTAGAAGCGTGCGCTCTGTGCCCGGCGAA	
	ATGCGGCTGGCCTCTATCGCCTTCAATCACCCCATCCAGGT	
	GGACCAGCTGAACTCCAGCTACTTCAAGCTGAGCATCCCC	
	ACCAACTTCAGCTTCGGCGTGACCCAGGAGTACATCCAGA	
	CCACAATCCAGAAAGTGACCGTGGACTGCAAGCAGTACGT	
	GTGCAACGGCTTTCAGAAGTGCGAACAGCTGCTGCGCGAG	
	TACGGCCAGTTCTGCAGCAAGATCAACCAGGCCCTGCACG	
	GCGCCAACCTGAGACAGGATGACAGCGTGCGGAACCTGTT	
	CGCCAGCGTGAAAAGCAGCCAGTCCAGCCCCATCATCCCT	
	GGCTTCGGCGGCGACTTTAACCTGACCCTGCTGGAACCTG	
	TGTCCATCAGCACCGGCTCCAGAAGCGCCAGATCCGCCAT	
	CGAGGACCTGCTGTTCGACAAAGTGACCATTGCCGACCCC	
	GGCTACATGCAGGGCTACGACGATTGCATGCAGCAGGGCC	
	CAGCCAGCGCCAGGGATCTGATCTGTGCCCAGTATGTGGC	
	CGGCTACAAGGTGCTGCCCCCCCTGATGGACGTGAACATG	
	GAAGCCGCCTACACCTCCAGCCTGCTGGGCTCTATTGCTG	
	GCGTGGGATGGACAGCCGGCCTGTCTAGCTTTGCCGCCAT	
	CCCTTTCGCCCAGAGCATCTTCTACCGGCTGAACGGCGTG	
	GGCATCACACAACAGGTGCTGAGCGAGAACCAGAAGCTG	
	ATCGCCAACAAGTTTAACCAGGCACTGGGCGCCATGCAGA	
	CCGGCTTCACCACCACCAACGAGGCCTTCAGAAAGGTGCA	
	GGACGCCGTGAACAACAACGCCCAGGCTCTGAGCAAGCT	
	GGCCTCCGAGCTGAGCAATACCTTCGGCGCCATCAGCGCC	
	TCCATCGGCGACATCATCCAGCGGCTGGACGTGCTGGAAC	
	AGGACGCCCAGATCGACCGGCTGATCAACGGCAGACTGA	
	CCACCCTGAACGCCTTCGTGGCACAGCAGCTCGTGCGGAG	
	CGAATCTGCCGCTCTGTCTGCTCAGCTGGCCAAGGACAAA	
	GTGAACGAGTGCGTGAAGGCCCAGTCCAAGCGGAGCGGC	
	TTTTGTGGCCAGGGCACCCACATCGTGTCCTTCGTCGTGAA	
	TGCCCCCAACGGCCTGTACTTTATGCACGTGGGCTATTACC	
	CCAGCAACCACATCGAGGTGGTGTCCGCCTATGGCCTGTG	
	CGACGCCGCCAATCCTACCAACTGTATCGCCCCCGTGAAC	
	GGCTACTTCATCAAGACCAACAACACCCGGATCGTGGACG	
	AGTGGTCCTACACAGGCAGCAGCTTCTACGCCCCCGAGCC	
	CATCACCTCCCTGAACACCAAATACGTGGCCCCCCAAGTG	
	ACATACCAGAACATCTCCACCAACCTGCCCCCTCCACTGC	
	TGGGAAATTCCACCGGCATCGACTTCCAGGACGAGCTGGA	
	CGAGTTCTTCAAGAACGTGTCCACCTCCATCCCCAACTTCG	
	GCAGCCTGACCCAGATCAACACCACTCTGCTGGACCTGAC	
	CTACGAGATGCTGTCCCTGCAACAGGTCGTGAAAGCCCTG	
	AACGAGAGCTACATCGACCTGAAAGAGCTGGGGAACTAC	
	ACCTACTACAACAAGTGGCCTTGGTACATTTGGCTGGGCT	
	TTATCGCCGGCCTGGTGGCCCTGGCCCTGTGCGTGTTCTTC	
	ATCCTGTGCTGCACCGGCTGCGGCACCAATTGCATGGGCA	
	AGCTGAAATGCAACCGGTGCTGCGACAGATACGAGGAAT	
	ACGACCTGGAACCTCACAAAGTGCATGTGCAC	

TABLE 10-continued

Betacoronavirus Nucleic Acid Sequence

Strain	Nucleic Acid Sequence	SEQ ID NO:
Betacoronavirus mRNA Sequences		
gb|KJ156934.1|: 21405-25466 Middle East respiratory syndrome coronavirus isolate Riyadh_14_2013, spike protein (nucleotide)	AUGAUACACUCAGUGUUUCUACUGAUGUUCUUGUUAAC ACCUACAGAAAGUUACGUUGAUGUAGGGCCAGAUUCUG UUAAGUCUGCUUGUAUUGAGGUUGAUAUACAACAGACC UUCUUUGAUAAAACUUGGCCUAGGCCAAUUGAUGUUUC UAAGGCUGACGGUAUUAUAUACCCUCAAGGCCGUACAU AUUCUAACAUAACUAUCACUUAUCAAGGUCUUUUUCCCU AUCAGGGAGACCAUGGUGAUAUGUAUGUUUACUCUGCA GGACAUGCUACAGGCACAACUCCACAAAAGUUGUUUGU AGCUAACUAUUCUCAGGACGUCAAACAGUUUGCUAAUG GGUUUGUCGUCCGUAUAGGAGCAGCUGCCAAUUCCACUG GCACUGUUAUUAUUAGCCCAUCUACCAGCGCUACUAUAC GAAAAAUUUACCCUGCUUUUAUGCUGGGUUCUUCAGUU GGUAAUUUCUCAGAUGGUAAAAUGGGCCGCUUCUUCAA UCAUACUCUAGUUCUUUUGCCCGAUGGAUGUGGCACUU UACUUAGAGCUUUUUAUUGUAUUCUAGAGCCUCGCUCU GGAAAUCAUUGUCCUGCUGGCAAUUCCUAUACUUCUUU UGCCACUUAUCACACUCCUGCAACAGAUUGUUCUGAUGG CAAUUACAAUCGUAAUGCCAGUCUGAACUCUUUUAAGG AGUAUUUUAAUUUACGUAACUGCACCUUUAUGUACACU UAUAACAUUACCGAAGAUGAGAUUUUAGAGUGGUUUGG CAUUACACAAACUGCUCAAGGUGUUCACCUCUUCUCAUC UCGGUAUGUUGAUUUGUACGGCGGCAAUAUGUUUCAAU UUGCCACCUUGCCUGUUUAUGAUACUAUUAAGUAUUAU UCUAUCAUUCCUCACAGUAUUCGUUCUAUCCAAAGUGAU AGAAAAGCUUGGGCUGCCUUCUACGUAUAUAAACUUCA ACCGUUAACUUUCCUGUUGGAUUUUUCUGUUGAUGGUU AUAUACGCAGAGCUAUAGACUGUGGUUUUAAUGAUUUG UCACAACUCCACUGCUCAUAUGAAUCCUUCGAUGUUGAA UCUGGAGUUUAUUCAGUUUCGUCUUUCGAAGCAAAACC UUCUGGCUCAGUUGUGGAACAGGCUGAAGGUGUUGAAU GUGAUUUUUCACCUCUUCUGUCUGGCACACCUCCUCAGG UUUAUAAUUUCAAGCGUUUGGUUUUUACCAAUUGCAAU UAUAAUCUUACCAAAUUGCUUUCACUUUUUUCUGUGAA UGAUUUUACUUGUAGUCAAAUAUCUCCAGCAGCAAUUG CUAGCAACUGUUAUUCUUCACUGAUUUUGGAUUAUUUU UCAUACCCACUUAGUAUGAAAUCCGAUCUCAGUGUUAG UUCUGCUGGUCCAAUAUCCCAGUUUAAUUAUAAACAGU CCUUUUCUAAUCCCACAUGUUUGAUCUUAGCGACUGUUC CUCAUAACCUUACUACUAUUACUAAGCCUCUUAAGUACA GCUAUAUUAACAAGUGCUCUCGUCUUCUUUCUGAUGAU CGUACUGAAGUACCUCAGUUAGUGAACGCUAAUCAAUA CUCACCCUGUGUAUCCAUUGUCCCAUCCACUGUGUGGGA AGACGGUGAUUAUUAUAGGAAACAACUAUCUCCACUUG AAGGUGGUGGCUGGCUUGUUGCUAGUGGCUCAACUGUU GCCAUGACUGAGCAAUUACAGAUGGGCUUUGGUAUUAC AGUUCAAUAUGGUACAGACACCAAUAGUGUUUGCCCCA AGCUUGAAUUUGCUAAUGACACAAAAAUUGCCUCUCAA UUAGGCAAUUGCGUGGAAUAUUCCCUCUAUGGUGUUUC GGGCCGUGGUGUUUUUCAGAAUUGCACAGCUGUAGGUG UUCGACAGCAGCGCUUUGUUUAUGAUGCGUACCAGAAU UUAGUUGGCUAUUAUUCUGAUGAUGGCAACUACUACUG UCUGCGUGCUUGUGUUAGUGUUCCUGUUUCUGUCAUCU AUGAUAAAGAAACUAAAACCCACGCUACUCUAUUUGGU AGUGUUGCAUGUGAACACAUUUCUUCUACCAUGUCUCA AUACUCCCGUUCUACGCGAUCAAUGCUUAAACGGCGAGA UUCUACAUAUGGCCCCCUUCAGACACCUGUUGGUUGUGU CCUAGGACUUGUUAAUUCCCUCUUUGUUCGUAGAGGACU GCAAGUUGCCUCUCGGUCAAUCUCUCUGUGCUCUUCCUG ACACACCUAGUACUCUCACACCUCGCAGUGUGCGCUCUG UGCCAGGUGAAAUGCGCUUGGCAUCCAUUGCUUUUAAU CAUCCCAUUCAGGUUGAUCAACUUAAUAGUAGUUAUUU UAAAUUAAGUAUACCCACUAAUUUUUCCUUUGGUGUGA CUCAGGAGUACAUUCAGACAACCAUUCAGAAAGUUACU GUUGAUUGUAAACAGUACGUUUGCAAUGGUUUCCAGAA GUGUGAGCAAUUACUGCGCGAGUAUGGCCAGUUUUGUU CCAAAAUAAACCAGGCUCUCCAUGGUGCCAAUUUACGCC AGGAUGAUUCUGUACGUAAUUUGUUUGCGAGCGUGAAA AGCUCUCAAUCAUCUCCUAUCAUACCAGGUUUUGGAGGU GACUUUAAUUUGACACUUCUAGAACCUGUUUCUAUAUC UACUGGCAGUCGUAGUGCACGUAGUGCUAUUGAGGAUU UGCUAUUUGACAAAGUCACUAUAGCUGAUCCUGGUUAU AUGCAAGGUUACGAUGAUUGUAUGCAGCAAGGUCCAGC	65

TABLE 10-continued

Betacoronavirus Nucleic Acid Sequence

Strain	Nucleic Acid Sequence	SEQ ID NO:
	AUCAGCUCGUGAUCUUAUUUGUGCUCAAUAUGUGGCUG	
	GUUAUAAAGUAUUACCUCCUCUUAUGGAUGUUAAUAUG	
	GAAGCCGCGUAUACUUCAUCUUUGCUUGGCAGCAUAGCA	
	GGUGUUGGCUGGACUGCUGGCUUAUCCUCCUUUGCUGCU	
	AUUCCAUUUGCACAGAGUAUYUUUUAUAGGUUAAACGG	
	UGUUGGCAUUACUCAACAGGUUCUUUCAGAGAACCAAA	
	AGCUUAUUGCCAAUAAGUUUAAUCAGGCUCUGGGAGCU	
	AUGCAAACAGGCUUCACUACAACUAAUGAAGCUUUUCG	
	GAAGGUUCAGGAUGCUGUGAACAACAAUGCACAGGCUC	
	UAUCCAAAUUAGCUAGCGAGCUAUCUAAUACUUUUGGU	
	GCUAUUUCCGCCUCUAUUGGAGACAUCAUACAACGUCUU	
	GAUGUUCUCGAACAGGACGCCCAAAUAGACAGACUUAU	
	UAAUGGCCGUUUGACAACACUAAAUGCUUUUGUUGCAC	
	AGCAGCUUGUUCGUUCCGAAUCAGCUGCUCUUUCCGCUC	
	AAUUGGCUAAAGAUAAAGUCAAUGAGUGUGUCAAGGCA	
	CAAUCCAAGCGUUCUGGAUUUUGCGGUCAAGGCACACAU	
	AUAGUGUCCUUUGUUGUAAAUGCCCCUAAUGGCCUUUA	
	CUUUAUGCAUGUUGGUUAUUACCCUAGCAACCACAUUG	
	AGGUUGUUUCUGCUUAUGGUCUUUGCGAUGCAGCUAAC	
	CCUACUAAUUGUAUAGCCCCUGUUAAUGGCUACUUUAU	
	UAAAACUAAUAACACUAGGAUUGUUGAUGAGUGGUCAU	
	AUACUGGCUCGUCCUUCUAUGCACCUGAGCCCAUCACCU	
	CUCUUAAUACUAAGUAUGUUGCACCACAGGUGACAUACC	
	AAAACAUUUCUACUAACCUCCCUCCUCCCUCUUCUCGGCA	
	AUUCCACCGGGAUUGACUUCCAAGAUGAGUUGGAUGAG	
	UUUUUCAAAAAUGUUAGCACCAGUAUACCUAAUUUUGG	
	UUCUCUAACACAGAUUAAUACUACAUUACUCGAUCUUAC	
	CUACGAGAUGUUGUCUCUUCAACAAGUUGUUAAAGCCC	
	UUAAUGAGUCUUACAUAGACCUUAAAGAGCUUGGCAAU	
	UAUACUUAUUACAACAAAUGGCCGUGGUACAUUUGGCU	
	UGGUUUCAUUGCUGGGCUUGUUGCCUUAGCUCUAUGCG	
	UCUUCUUCAUACUGUGCUGCACUGGUUGUGGCACAAACU	
	GUAUGGGAAAACUUAAGUGUAAUCGUUGUUGUGAUAGA	
	UACGAGGAAUACGACCUCGAGCCGCAUAAGGUUCAUGU	
	UCACUAA	
MERS S FL SPIKE 2cEMC/2012 (XBaI change(U to G)) (nucleotide)	AUGAUACACUCAGUGUUUCUACUGAUGUUCUUGUUAAC	66
	ACCUACAGAAAGUUACGUUGAUGUAGGGCCAGAUUCUG	
	UUAAGUCUGCUUGUAUUGAGGUUGAUAUACAACAGACU	
	UUCUUUGAUAAAACUUGGCCUAGGCCAAUUGAUGUUUC	
	UAAGGCUGACGGUAUUAUAUACCCUCAAGGCCGUACAU	
	AUUCUAACAUAACUAUCACUUAUCAAGGUCUUUUUCCCU	
	AUCAGGGAGACCAUGGUGAUAUGUAUGUUUACUCUGCA	
	GGACAUGCUACAGGCACAACUCCACAAAAGUUGUUUGU	
	AGCUAACUAUUCUCAGGACGUCAAACAGUUUGCUAAUG	
	GGUUUGUCGUCCGUAUAGGAGCAGCUGCCAAUUCCACUG	
	GCACUGUUAUUAUUAGCCCAUCUACCAGCGCUACUAUAC	
	GAAAAAUUUACCCUGCUUUUAUGCUGGGUUCUUCAGUU	
	GGUAAUUUCUCAGAUGGUAAAAUGGGCCGCUUCUUCAA	
	UCAUACUCUAGUUCUUUUGCCCGAUGGAUGUGGCACUU	
	UACUUAGAGCUUUUUAUUGUAUUCUGGAGCCUCGCUCU	
	GGAAAUCAUUGUCCUGCUGGCAAUUCCUAUACUUCUUU	
	UGCCACUUAUCACACUCCUGCAACAGAUUGUUCUGAUGG	
	CAAUUACAAUCGUAAUGCCAGUCUGAACUCUUUUAAGG	
	AGUAUUUUAAUUUACGUAACUGCACCUUUAUGUACACU	
	UAUAACAUUACCGAAGAUGAGAUUUUAGAGUGGUUUGG	
	CAUUACACAAACUGCUCAAGGUGUUCACCUCUUCUCAUC	
	UCGGUAUGUUGAUUUGUACGGCGGCAAUAUGUUUCAAU	
	UUGCCACCUUGCCUGUUUAUGAUACUAUUAAGUAUUAU	
	UCUAUCAUUCCUCACAGUAUUCGUUCUAUCCAAAGUGAU	
	AGAAAAGCUUGGGCUGCCUUCUACGUAUAUAAACUUCA	
	ACCGUUAACUUUCCUGUUGGAUUUUUCUGUUGAUGGUU	
	AUAUACGCAGAGCUAUAGACUGUGGUUUUAAUGAUUUG	
	UCACAACUCCACUGCUCAUAUGAAUCCUUCGAUGUUGAA	
	UCUGGAGUUUAUUCAGUUUCGUCUUUCGAAGCAAAACC	
	UUCUGGCUCAGUUGUGGAACAGGCUGAAGGUGUUGAAU	
	GUGAUUUUUCACCUCUUCUGUCUGGCACACCUCCUCAGG	
	UUUAUAAUUUCAAGCGUUUGGUUUUUACCAAUUGCAAU	
	UAUAAUCUUACCAAAUUGCUUUCACUUUUUUCUGUGAA	
	UGAUUUUACUUGUAGUCAAAUAUCUCCAGCAGCAAUUG	
	CUAGCAACUGUUAUUCUUCACUGAUUUUGGAUUACUUU	
	UCAUACCCACUUAGUAUGAAAUCCGAUCUCAGUGUUAG	
	UUCUGCUGGUCCAAUAUCCCAGUUUAAUUAUAAACAGU	
	CCUUUUCUAAUCCCACAUGUUUGAUUUUAGCGACUGUUC	
	CUCAUAACCUUACUACUAUUACUAAGCCUCUUAAGUACA	

TABLE 10-continued

Betacoronavirus Nucleic Acid Sequence

Strain	Nucleic Acid Sequence	SEQ ID NO:
	GCUAUAUUAACAAGUGCUCUCGUCUUCUUUCUGAUGAU	
	CGUACUGAAGUACCUCAGUUAGUGAACGCUAAUCAAUA	
	CUCACCCUGUGUAUCCAUUGUCCCAUCCACUGUGUGGGA	
	AGACGGUGAUUAUUAUAGGAAACAACUAUCUCCACUUG	
	AAGGUGGUGGCUGGCUUGUUGCUAGUGGCUCAACUGUU	
	GCCAUGACUGAGCAAUUACAGAUGGGCUUUGGUAUUAC	
	AGUUCAAUAUGGUACAGACACCAAUAGUGUUUGCCCCA	
	AGCUUGAAUUUGCUAAUGACACAAAAAUUGCCUCUCAA	
	UUAGGCAAUUGCGUGGAAUAUUCCCCUCUAUGGUGUUUC	
	GGGCCGUGGUGUUUUUCAGAAUUGCACAGCUGUAGGUG	
	UUCGACAGCAGCGCUUUGUUUAUGAUGCGUACCAGAAU	
	UUAGUUGGCUAUUAUUCUGAUGAUGGCAACUACUACUG	
	UUUGCGUGCUUGUGUUAGUGUUCCUGUUUCUGUCAUCU	
	AUGAUAAAGAAACUAAAACCCACGCUACUCUAUUUGGU	
	AGUGUUGCAUGUGAACACAUUUCUUCUACCAUGUCUCA	
	AUACUCCCGUUCUACGCGAUCAAUGCUUAAACGGCGAGA	
	UUCUACAUAUGGCCCCCUUCAGACACCUGUUGGUUGUGU	
	CCUAGGACUUGUUAAUUCCUCUUUGUUCGUAGAGGACU	
	GCAAGUUGCCUCUUGGUCAAUCUCUCUGUGCUCUUCCUG	
	ACACACCUAGUACUCUCACACCUCGCAGUGUGCGCUCUG	
	UUCCAGGUGAAAUGCGCUUGGCAUCCAUUGCUUUUAAU	
	CAUCCUAUUCAGGUUGAUCAACUUAAUAGUAGUUAUUU	
	UAAAUUAAGUAUACCCACUAAUUUUUCCUUUGGUGUGA	
	CUCAGGAGUACAUUCAGACAACCAUUCAGAAAGUUACU	
	GUUGAUUGUAAACAGUACGUUUGCAAUGGUUUCCAGAA	
	GUGUGAGCAAUUACUGCGCGAGUAUGGCCAGUUUUGUU	
	CCAAAAUAAACCAGGCUCUCCAUGGUGCCAAUUUACGCC	
	AGGAUGAUUCUGUACGUAAUUUGUUUGCGAGCGUGAAA	
	AGCUCUCAAUCAUCUCCUAUCAUACCAGGUUUUGGAGGU	
	GACUUUAAUUUGACACUUCUGGAACCUGUUUCUAUAUC	
	UACUGGCAGUCGUAGUGCACGUAGUGCUAUUGAGGAUU	
	UGCUAUUUGACAAAGUCACUAUAGCUGAUCCUGGUUAU	
	AUGCAAGGUUACGAUGAUUGCAUGCAGCAAGGUCCAGC	
	AUCAGCUCGUGAUCUUAUUUGUGCUCAAUAUGUGGCUG	
	GUUACAAAGUAUUACCUCCUCUUAUGGAUGUUAAUAUG	
	GAAGCCGCGUAUACUUCAUCUUUGCUUGGCAGCAUAGCA	
	GGUGUUGGCUGGACUGCUGGCUUAUCCUCCUUUGCUGCU	
	AUUCCAUUUGCACAGAGUAUCUUUUAUAGGUUAAACGG	
	UGUUGGCAUUACUCAACAGGUUCUUUCAGAGAACCAAA	
	AGCUUAUUGCCAAUAAGUUUAAUCAGGCUCUGGGAGCU	
	AUGCAAACAGGCUUCACUACAACUAAUGAAGCUUUUCA	
	GAAGGUUCAGGAUGCUGUGAACAACAAUGCACAGGCUC	
	UAUCCAAAUUAGCUAGCGAGCUAUCUAAUACUUUUGGU	
	GCUAUUUCCGCCUCUAUUGGAGACAUCAUACAACGUCUU	
	GAUGUUCUCGAACAGGACGCCCAAAUAGACAGACUUAU	
	UAAUGGCCGUUUGACAACACUAAAUGCUUUUGUUGCAC	
	AGCAGCUUGUUCGUUCCGAAUCAGCUGCUCUUUCCGCUC	
	AAUUGGCUAAAGAUAAAGUCAAUGAGUGUGUCAAGGCA	
	CAAUCCAAGCGUUCUGGAUUUUGCGGUCAAGGCACACAU	
	AUAGUGUCCUUUGUUGUAAAUGCCCCUAAUGGCCUUUA	
	CUUCAUGCAUGUUGGUUAUUACCCUAGCAACCACAUUGA	
	GGUUGUUUCUGCUUAUGGUCUUUGCGAUGCAGCUAACC	
	CUACUAAUUGUAUAGCCCCUGUUAAUGGCUACUUUAUU	
	AAAACUAAUAACACUAGGAUUGUUGAUGAGUGGUCAUA	
	UACUGGCUCGUCCUUCUAUGCACCUGAGCCCAUUACCUC	
	CCUUAAUACUAAGUAUGUUGCACCACAGGUGACAUACCA	
	AAACAUUUCUACUAACCUCCCCUCCUCCUCUUCUCGGCAA	
	UUCCACCGGGAUUGACUUCCAAGAUGAGUUGGAUGAGU	
	UUUUCAAAAAUGUUAGCACCAGUAUACCUAAUUUUGGU	
	UCCCUAACACAGAUUAAUACUACAUUACUCGAUCUUACC	
	UACGAGAUGUUGUCUCUUCAACAAGUUGUUAAAGCCCU	
	UAAUGAGUCUUACAUAGACCUUAAAGAGCUUGGCAAUU	
	AUACUUAUUACAACAAAUGGCCGUGGUACAUUUGGCUU	
	GGUUUCAUUGCUGGGCUUGUUGCCUUAGCUCUAUGCGU	
	CUUCUUCAUACUGUGCUGCACUGGUUGUGGCACAAACUG	
	UAUGGGAAAACUUAAGUGUAAUCGUUGUUGUGAUAGAU	
	ACGAGGAAUACGACCUCGAGCCGCAUAAGGUUCAUGUUC	
	ACUAA	
Novel_MERS_S2_subunit_trimeric vaccine (nucleotide)	AUGAUCCACUCCGUGUUCCUCCUCAUGUUCCUGUUGACC	67
	CCCACUGAGUCAGACUGCAAGCUCCCGCUGGGACAGUCC	
	CUGUGUGCGCUGCCUGACACUCCUAGCACUCUGACCCCA	
	CGCUCCGUGCGGUCGGUGCCUGGCGAAAUGCGGCUGGCC	
	UCCAUCGCCUUCAAUCACCCAAUCCAAGUGGAUCAGCUG	
	AAUAGCUCGUAUUUCAAGCUGUCCAUCCCCACGAACUUC	

TABLE 10-continued

Betacoronavirus Nucleic Acid Sequence

Strain	Nucleic Acid Sequence	SEQ ID NO:
	UCGUUCGGGGUCACCCAGGAGUACAUCCAGACCACAAUU	
	CAGAAGGUCACCGUCGAUUGCAAGCAAUACGUGUGCAAC	
	GGCUUCCAGAAGUGCGAGCAGCUGCUGAGAGAAUACGG	
	GCAGUUUUGCAGCAAGAUCAACCAGGCGCUGCAUGGAGC	
	UAACUUGCGCCAGGACGACUCCGUGCGCAACCUCUUUGC	
	CUCUGUGAAGUCAUCCCAGUCCUCCCCAAUCAUCCCGGG	
	AUUCGGAGGGGACUUCAACCUGACCCUCCUGGAGCCCGU	
	GUCGAUCAGCACCGGUAGCAGAUCGGCGCGCUCAGCCAU	
	UGAAGAUCUUCUGUUCGACAAGGUCACCAUCGCCGAUCC	
	GGGCUACAUGCAGGGAUACGACGACUGUAUGCAGCAGG	
	GACCAGCCUCCGCGAGGGACCUCAUCUGCGCGCAAUACG	
	UGGCCGGGUACAAAGUGCUGCCUCCUCUGAUGGAUGUG	
	AACAUGGAGGCCGCUUAUACUUCGUCCCUGCUCGGCUCU	
	AUCGCCGGCGUGGGGUGGACCGCCGGCCUGUCCUCCUUC	
	GCCGCUAUCCCCUUUGCACAAUCCAUUUUCUACCGGCUC	
	AACGGCGUGGGCAUUACUCAACAAGUCCUGUCGGAGAAC	
	CAGAAGUUGAUCGCAAACAAGUUCAAUCAGGCCCUGGG	
	GGCCAUGCAGACUGGAUUCACUACGACUAACGAAGCGUU	
	CCAGAAGGUCCAGGACGCUGUGAACAACAACGCCCAGGC	
	GCUCUCAAAGCUGGCCUCCGAACUCAGCAACACCUUCGG	
	AGCCAUCAGCGCAUCGAUCGGUGACAUAAUUCAGCGGCU	
	GGACGUGCUGGAGCAGGACGCCCAGAUCGACCGCCUCAU	
	CAACGGACGGCUGACCACCUUGAAUGCCUUCGUGGCACA	
	ACAGCUGGUCCGGAGCGAAUCAGCGGCACUUUCCGCCCA	
	ACUCGCCAAGGACAAAGUCAACGAAUGCGUGAAGGCCCA	
	GUCCAAGAGGUCCGGUUUCUGCGGUCAAGGAACCCAUAU	
	UGUGUCCUUCGUCGUGAACGCGCCCAACGGUCUGUACUU	
	UAUGCACGUCGGCUACUACCCGAGCAAUCAUAUCGAAGU	
	GGUGUCCGCCUACGGCCUGUGCGAUGCCGCUAACCCCAC	
	UAACUGUAUUGCCCCUGUGAACGGAUAUUUUAUUAAGA	
	CCAACAACACCCGCAUUGUGGACGAAUGGUCAUACACCG	
	GUUCGUCCUUCUACGCGCCCGAGCCCAUCACUUCACUGA	
	ACACCAAAUACGUGGCUCCGCAAGUGACCUACCAGAACA	
	UCUCCACCAAUUUGCCGCCGCCGCUGCUCGGAAACAGCA	
	CCGGAAUUGAUUUCCAAGAUGAACUGGACGAAUUCUUC	
	AAGAACGUGUCCACUUCCAUUCCCAACUUCGGAAGCCUG	
	ACACAGAUCAACACCACCCUUCUCGACCUGACCUACGAG	
	AUGCUGAGCCUUCAACAAGUGGUCAAGGCCCUGAACGAG	
	AGCUACAUCGACCUGAAGGAGCUGGGCAACUAUACCUAC	
	UACAACAAGUGGCCGGACAAGAUUGAGGAGAUUCUGUC	
	GAAAAUCUACCACAUUGAAAACGAGAUCGCCAGAAUCA	
	AGAAGCUUAUCGGCGAAGCC	
MERS_S0_Full-length Spike protein (nucleotide, codon optimized)	AUGGAAACCCCUGCCCAGCUGCUGUUCCUGCUGCUGCUG	68
	UGGCUGCCUGAUACCACCGGCAGCUAUGUGGACGUGGGC	
	CCCGAUAGCGUGAAGUCCGCCUGUAUCGAAGUGGACAUC	
	CAGCAGACCUUUUUCGACAAGACCUGGCCCAGACCCAUC	
	GACGUGUCCAAGGCCGACGGCAUCAUCUAUCCACAAGGC	
	CGGACCUACAGCAACAUCACCAUUACCUACCAGGGCCUG	
	UUCCCAUAUCAAGGCGACCACGGCGAUAUGUACGUGUAC	
	UCUGCCGGCCACGCCACCGGCACCACACCCCAGAAACUG	
	UUCGUGGCCAACUACAGCCAGGACGUGAAGCAGUUCGCC	
	AACGGCUUCGUCGUGCGGAUUGGCGCCGCUGCCAAUAGC	
	ACCGGCACAGUGAUCAUCAGCCCCAGCACCAGCGCCACC	
	AUCCGGAAGAUCUACCCCGCCUUCAUGCUGGGCAGCUCC	
	GUGGGCAAUUUCAGCGACGGCAAGAUGGGCCGGUUCUU	
	CAACCACACCCUGGUGCUGCUGCCCGAUGGCUGUGGCAC	
	ACUGCUGAGAGCCUUCUACUGCAUCCUGGAACCCAGAAG	
	CGGCAACCACUGCCCUGCCGGCAAUAGCUACACCAGCUU	
	CGCCACCUACCACACACCCGCCACCGAUUGCUCCGACGG	
	CAACUACAACCGGAACGCCAGCCUGAACAGCUUCAAAGA	
	GUACUUCAACCUGCGGAACUGCACCUUCAUGUACACCUA	
	CAAUAUCACCGAGGACGAGAUCCUGGAAUGGUUCGGCA	
	UCACCCAGACCGCCCAGGGCGUGCACCUGUUCAGCAGCA	
	GAUACGUGGACCUGUACGGCGGCAACAUGUUCCAGUUU	
	GCCACCCUGCCCGUGUACGACACCAUCAAGUACUACAGC	
	AUCAUCCCCCACAGCAUCCGGUCCAUCCAGAGCGACAGA	
	AAAGCCUGGGCCGCCUUCUACGUGUACAAGCUGCAGCCC	
	CUGACCUUCCUGCUGGACUUCAGCGUGGACGGCUACAUC	
	AGACGGGCCAUCGACUGCGGCUUCAACGACCUGAGCCAG	
	CUGCACUGCUCCUACGAGAGCUUCGACGUGGAAAGCGGC	
	GUGUACAGCGUGUCCAGCUUCGAGGCCAAGCCUAGCGGC	
	AGCGUGGUGGAACAGGCUGAGGGCGUGGAAUGCGACUU	
	CAGCCCUCUGCUGAGCGGCACCCCUCCCCAGGUGUACAA	
	CUUCAAGCGGCUGGUGUUCACCAACUGCAAUUACAACCU	

TABLE 10-continued

Betacoronavirus Nucleic Acid Sequence

Strain	Nucleic Acid Sequence	SEQ ID NO:
	GACCAAGCUGCUGAGCCUGUUCUCCGUGAACGACUUCAC	
	CUGUAGCCAGAUCAGCCCUGCCGCCAUUGCCAGCAACUG	
	CUACAGCAGCCUGAUCCUGGACUACUUCAGCUACCCCCU	
	GAGCAUGAAGUCCGAUCUGAGCGUGUCCUCCGCCGGACC	
	CAUCAGCCAGUUCAACUACAAGCAGAGCUUCAGCAACCC	
	UACCUGCCUGAUUCUGGCCACCGUGCCCCACAAUCUGAC	
	CACCAUCACCAAGCCCCUGAAGUACAGCUACAUCAACAA	
	GUGCAGCAGACUGCUGUCCGACGACCGGACCGAAGUGCC	
	CCAGCUCGUGAACGCCAACCAGUACAGCCCCUGCGUGUC	
	CAUCGUGCCCAGCACCGUGUGGGAGGACGGCGACUACUA	
	CAGAAAGCAGCUGAGCCCCCUGGAAGGCGGCGGAUGGCU	
	GGUGGCUUCUGGAAGCACAGUGGCCAUGACCGAGCAGCU	
	GCAGAUGGGCUUUGGCAUCACCGUGCAGUACGGCACCGA	
	CACCAACAGCGUGUGCCCCAAGCUGGAAUUCGCCAAUGA	
	CACCAAGAUCGCCAGCCAGCUGGGAAACUGCGUGGAAUA	
	CUCCCUGUAUGGCGUGUCCGGACGGGGCGUGUUCCAGAA	
	UUGCACAGCAGUGGGAGUGCGGCAGCAGAGAUUCGUGU	
	ACGAUGCCUACCAGAACCUCGUGGGCUACUACAGCGACG	
	ACGGCAAUUACUACUGCCUGCGGGCCUGUGUGUCCGUGC	
	CCGUGUCCGUGAUCUACGACAAAGAGACAAAGACCCACG	
	CCACACUGUUCGGCUCCGUGGCCUGCGAGCACAUCAGCU	
	CCACCAUGAGCCAGUACUCCCGCUCCACCCGGUCCAUGC	
	UGAAGCGGAGAGAUAGCACCUACGGCCCCCUGCAGACAC	
	CUGUGGGAUGUGUGCUGGGCCUCGUGAACAGCUCCCUGU	
	UUGUGGAAGAUUGCAAGCUGCCCCUGGGCCAGAGCCUGU	
	GUGCCCUGCCAGAUACCCCUAGCACCCUGACCCCUAGAA	
	GCGUGCGCUCUGUGCCCGGCGAAAUGCGGCUGGCCUCUA	
	UCGCCUUCAAUCACCCCAUCCAGGUGGACCAGCUGAACU	
	CCAGCUACUUCAAGCUGAGCAUCCCCACCAACUUCAGCU	
	UCGGCGUGACCCAGGAGUACAUCCAGACCACAAUCCAGA	
	AAGUGACCGUGGACUGCAAGCAGUACGUGUGCAACGGC	
	UUUCAGAAGUGCGAACAGCUGCUGCGCGAGUACGGCCAG	
	UUCUGCAGCAAGAUCAACCAGGCCCUGCACGGCGCCAAC	
	CUGAGACAGGAUGACAGCGUGCGGAACCUGUUCGCCAGC	
	GUGAAAAGCAGCCAGUCCAGCCCCAUCAUCCCUGGCUUC	
	GGCGGCGACUUUAACCUGACCCUGCUGGAACCUGUGUCC	
	AUCAGCACCGGCUCCAGAAGCGCCAGAUCCGCCAUCGAG	
	GACCUGCUGUUCGACAAAGUGACCAUUGCCGACCCCGGC	
	UACAUGCAGGGCUACGACGAUUGCAUGCAGCAGGGCCCA	
	GCCAGCGCCAGGGAUCUGAUCUGUGCCCAGUAUGUGGCC	
	GGCUACAAGGUGCUGCCCCCCCCUGAUGGACGUGAACAUG	
	GAAGCCGCCUACACCUCCAGCCUGCUGGGCUCUAUUGCU	
	GGCGUGGGAUGGACAGCCGGCCUGUCUAGCUUUGCCGCC	
	AUCCCUUUCGCCCAGAGCAUCUUCUACCGGCUGAACGGC	
	GUGGGCAUCACACAACAGGUGCUGAGCGAGAACCAGAA	
	GCUGAUCGCCAACAAGUUUAACCAGGCACUGGGCGCCAU	
	GCAGACCGGCUUCACCACCACCAACGAGGCCUUCAGAAA	
	GGUGCAGGACGCCGUGAACAACAACGCCCAGGCUCUGAG	
	CAAGCUGGCCUCCGAGCUGAGCAAUACCUUCGGCGCCAU	
	CAGCGCCUCCAUCGGCGACAUCAUCCAGCGGCUGGACGU	
	GCUGGAACAGGACGCCCAGAUCGACCGGCUGAUCAACGG	
	CAGACUGACCACCCUGAACGCCUUCGUGGCACAGCAGCU	
	CGUGCGGAGCGAAUCUGCCGCUCUGUCUGCUCAGCUGGC	
	CAAGGACAAAGUGAACGAGUGCGUGAAGGCCCAGUCCA	
	AGCGGAGCGGCUUUUGUGGCCAGGGCACCCACAUCGUGU	
	CCUUCGUCGUGAAUGCCCCCAACGGCCUGUACUUUAUGC	
	ACGUGGGCUAUUACCCCAGCAACCACAUCGAGGUGGUGU	
	CCGCCUAUGGCCUGUGCGACGCCGCCAAUCCUACCAACU	
	GUAUCGCCCCCGUGAACGGCUACUUCAUCAAGACCAACA	
	ACACCCGGAUCGUGGACGAGUGGUCCUACACAGGCAGCA	
	GCUUCUACGCCCCCGAGCCCAUCACCUCCCUGAACACCA	
	AAUACGUGGCCCCCCAAGUGACAUACCAGAACAUCUCCA	
	CCAACCUGCCCCCUCCACUGCUGGGAAAUUCCACCGGCA	
	UCGACUUCCAGGACGAGCUGGACGAGUUCUUCAAGAACG	
	UGUCCACCUCCAUCCCCAACUUCGGCAGCCUGACCCAGA	
	UCAACACCACUCUGCUGGACCUGACCUACGAGAUGCUGU	
	CCCUGCAACAGGUCGUGAAAGCCCUGAACGAGAGCUACA	
	UCGACCUGAAAGAGCUGGGGAACUACACCUACUACAACA	
	AGUGGCCUUGGUACAUUUGGCUGGGCUUUAUCGCCGGCC	
	UGGUGGCCCUGGCCCUGUGCGUGUUCUUCAUCCUGUGCU	
	GCACCGGCUGCGGCACCAAUUGCAUGGGCAAGCUGAAAU	
	GCAACCGGUGCUGCGACAGAUACGAGGAAUACGACCUGG	
	AACCUCACAAAGUGCAUGUGCAC	

TABLE 11

Betacoronavirus Amino Acid Sequences

Strain	Amino Acid Sequence	SEQ ID NO:
gb|KJ156934.1|: 21405-25466 Middle East respiratory syndrome coronavirus isolate Riyadh_14_2013, spike protein (amino acid)	MIHSVFLLMFLLTPTESYVDVGPDSVKSACIEVDIQQTFFDKT WPRPIDVSKADGIIYPQGRTYSNITITYQGLFPYQGDHGDMY VYSAGHATGTTpQKLFVANYSQDVKQFANGFVVRIGAAANS TGTVIISPSTSATIRKIYPAFMLGSSVGNFSDGKMGRFFNHTL VLLPDGCGTLLRAFYCILEPRSGNHCPAGNSYTSFATYHTPA TDCSDGNYNRNASLNSFKEYFNLRNCTFMYTYNITEDEILEW FGITQTAQGVHLFSSRYVDLYGGNMFQFATLPVYDTIKYYSII PHSIRSIQSDRKAWAAFYVYKLQPLTFLLDFSVDGYIRRAIDC GFNDLSQLHCSYESFDVESGVYSVSSFEAKPSGSVVEQAEGV ECDFSPLLSGTPPQVYNFKRLVFTNCNYNLTKLLSLFSVNDFt CSQISPAAIASNCYSSLILDYFSYPLSMKSDLSVSSAGPISQFN YKQSFSNPTCLILATVPHNLTTITKPLKYSYINKCSRLLSDDRT EVPQLVNANQYSPCVSIVPSTVWEDGDYYRKQLSPLEGGGW LVASGSTVAMTEQLQMGFGITVQYGTDTNSVCPKLEFANDT KIASQLGNCVEYSLYGVSGRGVFQNCTAVGVRQQRFVYDA YQNLVGYYSDDGNYYCLRACVSVPVSVIYDKETKTHATLFG SVACEHISSTMSQYSRSTRSMLKRRDSTYGPLQTPVGCVLGL VNSSLFVEDCKLPLGQSLCALPDTPSTLTPRSVRSVPGEMRLA SIAFNHPIQVDQLNSSYFKLSIPTNFSFGVTQEYIQTTIQKVTV DCKQYVCNGFQKCEQLLREYGQFCSKINqALHGANLRQDDS VRNLFASVKSSQSSPIIPGFGGDFNLTLLEPVSISTGSRSARSAI EDLLFDKVTIADPGYMQGYDDCMQQGPASARDLICAQYVA GYKVLPPLMDVNMEAAYTSSLLGSIAGVGWTAGLSSFAAIPF AQSIFYRLNGVGITQQVLSENQKLIANKFNQALGAMQTGFTT TNEAFrKVQDAVNNNAQALSKLASELSNTFGAISASIGDIIQR LDVLEQDAQIDRLINGRLTTLNAFVAQQLVRSESAALSAQLA KDKVNECVKAQSKRSGFCGQGTHIVSFVVNAPNGLYFMHV GYYPSNHIEVVSAYGLCDAANPTNCIAPVNGYFIKTNNTRIV DEWSYTGSSFYAPEPITSLNTKYVAPQVTYQNISTNLPPPLLG NSTGIDFQDELDEFFKNVSTSIPNFGSLTQINTTLLDLTYEMLS LQQVVKALNESYIDLKELGNYTYYNKWPWYIWLGFIAGLVA LALCVFFILCCTGCGTNCMGKLKCNRCCDRYEEYDLEPHKV HVH	24
MERS S FL SPIKE 2cEMC/2012 (XBaI change(T to G)) (amino acid)	MIHSVFLLMFLLTPTESYVDVGPDSVKSACIEVDIQQTFFDKT WPRPIDVSKADGIIYPQGRTYSNITITYQGLFPYQGDHGDMY VYSAGHATGTTPQKLFVANYSQDVKQFANGFVVRIGAAANS TGTVIISPSTSATIRKIYPAFMLGSSVGNFSDGKMGRFFNHTL VLLPDGCGTLLRAFYCILEPRSGNHCPAGNSYTSFATYHTPA TDCSDGNYNRNASLNSFKEYFNLRNCTFMYTYNITEDEILEW FGITQTAQGVHLFSSRYVDLYGGNMFQFATLPVYDTIKYYSII PHSIRSIQSDRKAWAAFYVYKLQPLTFLLDFSVDGYIRRAIDC GFNDLSQLHCSYESFDVESGVYSVSSFEAKPSGSVVEQAEGV ECDFSPLLSGTPPQVYNFKRLVFTNCNYNLTKLLSLFSVNDFT CSQISPAAIASNCYSSLILDYFSYPLSMKSDLSVSSAGPISQFN YKQSFSNPTCLILATVPHNLTTITKPLKYSYINKCSRLLSDDRT EVPQLVNANQYSPCVSIVPSTVWEDGDYYRKQLSPLEGGGW LVASGSTVAMTEQLQMGFGITVQYGTDTNSVCPKLEFANDT KIASQLGNCVEYSLYGVSGRGVFQNCTAVGVRQQRFVYDA YQNLVGYYSDDGNYYCLRACVSVPVSVIYDKETKTHATLFG SVACEHISSTMSQYSRSTRSMLKRRDSTYGPLQTPVGCVLGL VNSSLFVEDCKLPLGQSLCALPDTPSTLTPRSVRSVPGEMRLA SIAFNHPIQVDQLNSSYFKLSIPTNFSFGVTQEYIQTTIQKVTV DCKQYVCNGFQKCEQLLREYGQFCSKINQALHGANLRQDDS VRNLFASVKSSQSSPIIPGFGGDFNLTLLEPVSISTGSRSARSAI EDLLFDKVTIADPGYMQGYDDCMQQGPASARDLICAQYVA GYKVLPPLMDVNMEAAYTSSLLGSIAGVGWTAGLSSFAAIPF AQSIFYRLNGVGITQQVLSENQKLIANKFNQALGAMQTGFTT TNEAFQKVQDAVNNNAQALSKLASELSNTFGAISASIGDIIQR LDVLEQDAQIDRLINGRLTTLNAFVAQQLVRSESAALSAQLA KDKVNECVKAQSKRSGFCGQGTHIVSFVVNAPNGLYFMHV GYYPSNHIEVVSAYGLCDAANPTNCIAPVNGYFIKTNNTRIV DEWSYTGSSFYAPEPITSLNTKYVAPQVTYQNISTNLPPPLLG NSTGIDFQDELDEFFKNVSTSIPNFGSLTQINTTLLDLTYEMLS LQQVVKALNESYIDLKELGNYTYYNKWPWYIWLGFIAGLVA LALCVFFILCCTGCGTNCMGKLKCNRCCDRYEEYDLEPHKV HVH	25
Novel_MERS_S2_subunit_trimeric vaccine (amino acid)	MIHSVFLLMFLLTPTESDCKLPLGQSLCALPDTPSTLTPRSVR SVPGEMRLASIAFNHPIQVDQLNSSYFKLSIPTNFSFGVTQEYI QTTIQKVTVDCKQYVCNGFQKCEQLLREYGQFCSKINQALH GANLRQDDSVRNLFASVKSSQSSPIIPGFGGDFNLTLLEPVSIS TGSRSARSAIEDLLFDKVTIADPGYMQGYDDCMQQGPASAR DLICAQYVAGYKVLPPLMDVNMEAAYTSSLLGSIAGVGWTA GLSSFAAIPFAQSIFYRLNGVGITQQVLSENQKLIANKFNQAL	26

TABLE 11-continued

Betacoronavirus Amino Acid Sequences

Strain	Amino Acid Sequence	SEQ ID NO:
	GAMQTGFTTTNEAFQKVQDAVNNNAQALSKLASELSNTFG AISASIGDIIQRLDVLEQDAQIDRLINGRLTTLNAFVAQQLVRS ESAALSAQLAKDKVNECVKAQSKRSGFCGQGTHIVSFVVNA PNGLYFMHVGYYPSNHIEVVSAYGLCDAANPTNCIAPVNGY FIKTNNTRIVDEWSYTGSSFYAPEPITSLNTKYVAPQVTYQNI STNLPPPLLGNSTGIDFQDELDEFFKNVSTSIPNFGSLTQINTTL LDLTYEMLSLQQVVKALNESYIDLKELGNYTYYNKWPDKIE EILSKIYHIENEIARIKKLIGEA	
Isolate Al-Hasa_1_2013 (NCBI accession #AGN70962)	MIHSVFLLMFLLTPTESYVDVGPDSVKSACIEVDIQQTFFDKT WPRPIDVSKADGIIYPQGRTYSNITITYQGLFPYQGDHGDMY VYSAGHATGTTPQKLFVANYSQDVKQFANGFVVRIGAAANS TGTVIISPSTSATIRKIYPAFMLGSSVGNFSDGKMGRFFNHTL VLLPDGCGTLLRAFYCILEPRSGNHCPAGNSYTSFATYHTPA TDCSDGNYNRNASLNSFKEYFNLRNCTFMYTYNITEDEILEW FGITQTAQGVHLFSSRYVDLYGGNMFQFATLPVYDTIKYYSII PHSIRSIQSDRKAWAAFYVYKLQPLTFLLDFSVDGYIRRAIDC GFNDLSQLHCSYESFDVESGVYSVSSFEAKPSGSVVEQAEGV ECDFSPLLSGTPPQVYNFKRLVFTNCNYNLTKLLSLFSVNDFT CSQISPAAIASNCYSSLILDYFSYPLSMKSDLSVSSAGPISQFN YKQSFSNPTCLILATVPHNLTTITKPLKYSYINKCSRLLSDDRT EVPQLVNANQYSPCVSIVPSTVWEDGDYYRKQLSPLEGGGW LVASGSTVAMTEQLQMGFGITVQYGTDTNSVCPKLEFANDT KIASQLGNCVEYSLYGVSGRGVFQNCTAVGVRQQRFVYDA YQNLVGYYSDDGNYYCLRACVSVPVSVIYDKETKTHATLFG SVACEHISSTMSQYSRSTRSMLKRRDSTYGPLQTPVGCVLGL VNSSLFVEDCKLPLGQSLCALPDTPSTLTPRSVRSVPGEMRLA SIAFNHPIQVDQLNSSYFKLSIPTNFSFGVTQEYIQTTIQKVTV DCKQYVCNGFQKCEQLLREYGQFCSKINQALHGANLRQDDS VRNLFASVKSSQSSPIIPGFGGDFNLTLLEPVSISTGSRSARSAI EDLLFDKVTIADPGYMQGYDDCMQQGPASARDLICAQYVA GYKVLPPLMDVNMEAAYTSSLLGSIAGVGWTAGLSSFAAIPF AQSIFYRLNGVGITQQVLSENQKLIANKFNQALGAMQTGFTT TNEAFRKVQDAVNNNAQALSKLASELSNTFGAISASIGDIIQR LDVLEQDAQIDRLINGRLTTLNAFVAQQLVRSESAALSAQLA KDKVNECVKAQSKRSGFCGQGTHIVSFVVNAPNGLYFMHV GYYPSNHIEVVSAYGLCDAANPTNCIAPVNGYFIKTNNTRIV DEWSYTGSSFYAPEPITSLNTKYVAPHVTYQNISTNLPPPLLG NSTGIDFQDELDEFFKNVSTSIPNFGSLTQINTTLLDLTYEMLS LQQVVKALNESYIDLKELGNYTYYNKWPWYIWLGFIAGLVA LALCVFFILCCTGCGTNCMGKLKCNRCCDRYEEYDLEPHKV HVH	27
Middle East respiratory syndrome coronavirus S protein UniProtKB-R9UQ53	MIHSVFLLMFLLTPTESYVDVGPDSVKSACIEVDIQQTFFDKT WPRPIDVSKADGIIYPQGRTYSNITITYQGLFPYQGDHGDMY VYSAGHATGTTPQKLFVANYSQDVKQFANGFVVRIGAAANS TGTVIISPSTSATIRKIYPAFMLGSSVGNFSDGKMGRFFNHTL VLLPDGCGTLLRAFYCILEPRSGNHCPAGNSYTSFATYHTPA TDCSDGNYNRNASLNSFKEYFNLRNCTFMYTYNITEDEILEW FGITQTAQGVHLFSSRYVDLYGGNMFQFATLPVYDTIKYYSII PHSIRSIQSDRKAWAAFYVYKLQPLTFLLDFSVDGYIRRAIDC GFNDLSQLHCSYESFDVESGVYSVSSFEAKPSGSVVEQAEGV ECDFSPLLSGTPPQVYNFKRLVFTNCNYNLTKLLSLFSVNDFT CSQISPAAIASNCYSSLILDYFSYPLSMKSDLSVSSAGPISQFN YKQSFSNPTCLILATVPHNLTTITKPLKYSYINKCSRLLSDDRT EVPQLVNANQYSPCVSIVPSTVWEDGDYYRKQLSPLEGGGW LVASGSTVAMTEQLQMGFGITVQYGTDTNSVCPKLEFANDT KIASQLGNCVEYSLYGVSGRGVFQNCTAVGVRQQRFVYDA YQNLVGYYSDDGNYYCLRACVSVPVSVIYDKETKTHATLFG SVACEHISSTMSQYSRSTRSMLKRRDSTYGPLQTPVGCVLGL VNSSLFVEDCKLPLGQSLCALPDTPSTLTPRSVRSVPGEMRLA SIAFNHPIQVDQLNSSYFKLSIPTNFSFGVTQEYIQTTIQKVTV DCKQYVCNGFQKCEQLLREYGQFCSKINQALHGANLRQDDS VRNLFASVKSSQSSPIIPGFGGDFNLTLLEPVSISTGSRSARSAI EDLLFDKVTIADPGYMQGYDDCMQQGPASARDLICAQYVA GYKVLPPLMDVNMEAAYTSSLLGSIAGVGWTAGLSSFAAIPF AQSIFYRLNGVGITQQVLSENQKLIANKFNQALGAMQTGFTT TNEAFRKVQDAVNNNAQALSKLASELSNTFGAISASIGDIIQR LDVLEQDAQIDRLINGRLTTLNAFVAQQLVRSESAALSAQLA KDKVNECVKAQSKRSGFCGQGTHIVSFVVNAPNGLYFMHV GYYPSNHIEVVSAYGLCDAANPTNCIAPVNGYFIKTNNTRIV DEWSYTGSSFYAPEPITSLNTKYVAPHVTYQNISTNLPPPLLG NSTGIDFQDELDEFFKNVSTSIPNFGSLTQINTTLLDLTYEMLS LQQVVKALNESYIDLKELGNYTYYNKWPWYIWLGFIAGLVA	

TABLE 11-continued

Betacoronavirus Amino Acid Sequences

Strain	Amino Acid Sequence	SEQ ID NO:
	LALCVFFILCCTGCGTNCMGKLKCNRCCDRYEEYDLEPHKV HVH	
Human SARS coronavirus (SARS-CoV) (Severe acute respiratory syndrome coronavirus) Spike glycoprotein UniProtKB-P59594	MFIFLLFLTLTSGSDLDRCTTFDDVQAPNYTQHTSSMRGVYY PDEIFRSDTLYLTQDLFLPFYSNVTGFHTINHTFGNPVIPFKDG IYFAATEKSNVVRGWVFGSTMNNKSQSVIIINNSTNVVIRAC NFELCDNPFFAVSKPMGTQTHTMIFDNAFNCTFEYISDAFSLD VSEKSGNFKHLREFVFKNKDGFLYVYKGYQPIDVVRDLPSGF NTLKPIFKLPLGINITNFRAILTAFSPAQDIWGTSAAAYFVGYL KPTTFMLKYDENGTITDAVDCSQNPLAELKCSVKSFEIDKGI YQTSNFRVVPSGDVVRFPNITNLCPFGEVFNATKFPSVYAWE RKKISNCVADYSVLYNSTFFSTFKCYGVSATKLNDLCFSNVY ADSFVVKGDDVRQIAPGQTGVIADYNYKLPDDFMGCVLAW NTRNIDATSTGNYNYKYRYLRHGKLRPFERDISNVPFSPDGK PCTPPALNCYWPLNDYGFYTTTGIGYQPYRVVVLSFELLNAP ATVCGPKLSTDLIKNQCVNFNFNGLTGTGVLTPSSKRFQPFQ QFGRDVSDFTDSVRDPKTSEILDISPCSFGGVSVITPGTNASSE VAVLYQDVNCTDVSTAIHADQLTPAWRIYSTGNNVFQTQAG CLIGAEHVDTSYECDIPIGAGICASYHTVSLLRSTSQKSIVAYT MSLGADSSIAYSNNTIAIPTNFSISITTEVMPVSMAKTSVDCN MYICGDSTECANLLLQYGSFCTQLNRALSGIAAEQDRNTREV FAQVKQMYKTPTLKYFGGFNFSQILPDPLKPTKRSFIEDLLFN KVTLADAGFMKQYGECLGDINARDLICAQKFNGLTVLPPLL TDDMIAAYTAALVSGTATAGWTFGAGAALQIPFAMQMAYR FNGIGVTQNVLYENQKQIANQFNKAISQIQESLTTTSTALGKL QDVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDKVEAE VQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSEC VLGQSKRVDFCGKGYHLMSFPQAAPHGVVFLHVTYVPSQER NFTTAPAICHEGKAYFPREGVFVFNGTSWFITQRNFFSPQIITT DNTFVSGNCDVVIGIINNTVYDPLQPELDSFKEELDKYFKNH TSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE LGKYEQYIKWPWYVWLGFIAGLIAIVMVTILLCCMTSCCSCL KGACSCGSCCKFDEDDSEPVLKGVKLHYT	29
Human coronavirus OC43 (HCoV-OC43) Spike glycoprotein UniProtKB-P36334	MFLILLISLPTAFAVIGDLKCTSDNINDKDTGPPPISTDTVDVT NGLGTYYVLDRVYLNTTLFLNGYYPTSGSTYRNMALKGSVL LSRLWFKPPFLSDFINGIFAKVKNTKVIKDRVMYSEFPAITIGS TFVNTSYSVVVQPRTINSTQDGDNKLQGLLEVSVCQYNMCE YPQTICHPNLGNHRKELWHLDTGVVSCLYKRNFTYDVNAD YLYFHFYQEGGTFYAYFTDTGVVTKFLFNVYLGMALSHYYV MPLTCNSKLTLEYWVTPLTSRQYLLAFNQDGIIFNAEDCMSD FMSEIKCKTQSIAPPTGVYELNGYTVQPIADVYRRKPNLPNC NIEAWLNDKSVPSPLNWERKTFSNCNFNMSSLMSFIQADSFT CNNIDAAKIYGMCFSSITIDKFAIPNGRKVDLQLGNLGYLQSF NYRIDTTATSCQLYYNLPAANVSVSRFNPSTWNKRFGFIEDS VFKPRPAGVLTNHDVVYAQHCFKAPKNFCPCKLNGSCVGSG PGKNNGIGTCPAGTNYLTCDNLCTPDPITFTGTYKCPQTKSL VGIGEHCSGLAVKSDYCGGNSCTCRPQAFLGWSADSCLQGD KCNIFANFILHDVNSGLTCSTDLQKANTDIILGVCVNYDLYGI LGQGIFVEVNATYYNSWQNLLYDSNGNLYGFRDYIINRTFMI RSCYSGRVSAAFHANSSEPALLFRNIKCNYVFNNSLTRQLQPI NYFDSYLGCVVNAYNSTAISVQTCDLTVGSGYCVDYSKNRR SRGAITTGYRFTNFEPFTVNSVNDSLEPVGGLYEIQIPSEFTIG NMVEFIQTSSPKVTIDCAAFVCGDYAACKSQLVEYGSFCDNI NAILTEVNELLDTTQLQVANSLMNGVTLSTKLKDGVNFNVD DINFSPVLGCLGSECSKASSRSAIEDLLFDKVKLSDVGFVEAY NNCTGGAEIRDLICVQSYKGIKVLPPLLSENQISGYTLAATSA SLFPPWTAAAGVPFYLNVQYRINGLGVTMDVLSQNQKLIAN AFNNALYAIQEGFDATNSALVKIQAVVNANAEALNNLLQQL SNRFGAISASLQEILSRLDALEAEAQIDRLINGRLTALNAYVS QQLSDSTLVKFSAAQAMEKVNECVKSQSSRINFCGNGNHIIS LVQNAPYGLYFIHFSYVPTKYVTARVSPGLCIAGDRGIAPKS GYFVNVNNTWMYTGSGYYYPEPITENNVVVMSTCAVNYTK APYVMLNTSIPNLPDFKEELDQWFKNQTSVAPDLSLDYINVT FLDLQVEMNRLQEAIKVLNQSYINLKDIGTYEYYVKWPWYV WLLICLAGVAMLVLLFFICCCTGCGTSCFKKCGGCCDDYTG YQELVIKTSHDD	30
Human coronavirus HKU1 (isolate N5) (HCoV-HKU1) Spike glycoprotein	MFLIIFILPTTLAVIGDFNCTNSFINDYNKTIPRISEDVVDVSLG LGTYYVLNRVYLNTTLLFTGYFPKSGANFRDLALKGSIYLST LWYKPPFLSDFNNGIFSKVKNTKLYVNNTLYSEFSTIVIGSVF VNTSYTIVVQPHNGILEITACQYTMCEYPHTVCKSKGSIRNES WHIDSSEPLCLFKKNFTYNVSADWLYFHFYQERGVFYAYYA DVGMPTTFLFSLYLGTILSHYYVMPLTCNAISSNTDNETLEY	31

TABLE 11-continued

Betacoronavirus Amino Acid Sequences

Strain	Amino Acid Sequence	SEQ ID NO:
UniProtKB-Q0ZME7	WVTPLSRRQYLLNFDEHGVITNAVDCSSSFLSEIQCKTQSFAP NTGVYDLSGFTVKPVATVYRRIPNLPDCDIDNWLNNVSVPSP LNWERRIFSNCNFNLSTLLRLVHVDSFSCNNLDKSKIFGSCFN SITVDKFAIPNRRRDDLQLGSSGFLQSSNYKIDISSSSCQLYYS LPLVNVTINNFNPSSWNRRYGFGSFNLSSYDVVYSDHCFSVN SDFCPCADPSVVNSCAKSKPPSAICPAGTKYRHCDLDTTLYV KNWCRCSCLPDPISTYSPNTCPQKKVVVGIGEHCPGLGINEE KCGTQLNHSSCFCSPDAFLGWSFDSCISNNRCNIFSNFIFNGIN SGTTCSNDLLYSNTEISTGVCVNYDLYGITGQGIFKEVSAAY YNNWQNLLYDSNGNIIGFKDFLTNKTYTILPCYSGRVSAAFY QNSSSPALLYRNLKCSYVLNNISFISQPFYFDSYLGCVLNAVN LTSYSVSSCDLRMGSGFCIDYALPSSRRKRRGISSPYRFVTFEP FNVSFVNDSVETVGGLFEIQIPTNFTIAGHEEFIQTSSPKVTIDC SAFVCSNYAACHDLLSEYGTFCDNINSILNEVNDLLDITQLQV ANALMQGVTLSSNLNTNLHSDVDNIDFKSLLGCLGSQCGSSS RSLLEDLLFNKVKLSDVGFVEAYNNCTGGSEIRDLLCVQSFN GIKVLPPILSETQISGYTTAATVAAMFPPWSAAAGVPFSLNVQ YRINGLGVTMDVLNKNQKLIANAFNKALLSIQNGFTATNSAL AKIQSVVNANAQALNSLLQQLFNKFGAISSSLQEILSRLDNLE AQVQIDRLINGRTALNAYVSQQLSDITLIKAGASRAIEKVNE CVKSQSPRINFCGNGNHILSLVQNAPYGLLFIHFSYKPTSFKT VLVSPGLCLSGDRGIAPKQGYFIKQNDSWMFTGSSYYYPEPIS DKNVVFMNSCSVNFTKAPFIYLNNSIPNLSDFEAELSLWFKN HTSIAPNLTFNSHINATFLDLYYEMNVIQESIKSLNSSFINLKEI GTYEMYVKWPWYIWLLIVILFIIFLMILFFICCCTGCGSACFSK CHNCCDEYGGHNDFVIKASHDD	
Novel_SARS_S2	MFIFLLFLTLTSGSDLDRALSGIAAEQDRNTREVFAQVKQMY KTPTLKYFGGFNFSQILPDPLKPTKRSFIEDLLFNKVTLADAG FMKQYGECLGDINARDLICAQKFNGLTVLPPLLTDDMIAAYT AALVSGTATAGWTFGAGAALQIPFAMQMAYRFNGIGVTQN VLYENQKQIANQFNKAISQIQESLTTTSTALGKLQDVVNQNA QALNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITG RLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRV DFCGKGYHLMSFPQAAPHGVVFLHVTYVPSQERNFTTAPAIC HEGKAYFPREGVFVFNGTSWFITQRNFFSPQIITTDNTFVSGN CDVVIGIINNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLG DISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYI KWPWYVWLGFIAGLIAIVMVTILLCCMTSCCSCLKGACSCGS CCKFDEDDSEPVLKGVKLHYT	32
Novel_MERS_S2	MIHSVFLLMFLLTPTESDCKLPLGQSLCALPDTPSTLTPRSVR SVPGEMRLASIAFNHPIQVDQLNSSYFKLSIPTNFSFGVTQEYI QTTIQKVTVDCKQYVCNGFQKCEQLLREYGQFCSKINQALH GANLRQDDSVRNLFASVKSSQSSPIIPGFGGDFNLTLLEPVSIS TGSRSARSAIEDLLFDKVTIADPGYMQGYDDCMQQGPASAR DLICAQYVAGYKVLPPLMDVNMEAAYTSSLLGSIAGVGWTA GLSSFAAIPFAQSIFYRLNGVGITQQVLSENQKLIANKFNQAL GAMQTGFTTTNEAFQKVQDAVNNNAQALSKLASELSNTFG AISASIGDIIQRLDVLEQDAQIDRLINGRLTTLNAFVAQQLVRS ESAALSAQLAKDKVNECVKAQSKRSGFCGQGTHIVSFVVNA PNGLYFMHVGYYPSNHIEVVSAYGLCDAANPTNCIAPVNGY FIKTNNTRIVDEWSYTGSSFYAPEPITSLNTKYVAPQVTYQNI STNLPPPLLGNSTGIDFQDELDEFFKNVSTSIPNFGSLTQINTTL LDLTYEMLSLQQVVKALNESYIDLKELGNYTYYNKWP	33
Novel_Trimeric_SARS_S2	MFIFLLFLTLTSGSDLDRALSGIAAEQDRNTREVFAQVKQMY KTPTLKYFGGFNFSQILPDPLKPTKRSFIEDLLFNKVTLADAG FMKQYGECLGDINARDLICAQKFNGLTVLPPLLTDDMIAAYT AALVSGTATAGWTFGAGAALQIPFAMQMAYRFNGIGVTQN VLYENQKQIANQFNKAISQIQESLTTTSTALGKLQDVVNQNA QALNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITG RLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRV DFCGKGYHLMSFPQAAPHGVVFLHVTYVPSQERNFTTAPAIC HEGKAYFPREGVFVFNGTSWFITQRNFFSPQIITTDNTFVSGN CDVVIGIINNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLG DISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYI KWPWYVWLGFIAGLIAIVMVTILLCCMTSCCSCLKGACSCGS CCKFDEDDSEPVLKGVKLHYT	34

TABLE 12

Full-length Spike Glycoprotein Amino Acid Sequences (*Homo sapiens* strains)

GenBank Accession	Country	Collection Date	Release Date	Virus Name
AFY13307	United Kingdom	2012 Sep. 11	2012 Dec. 5	Betacoronavirus England 1, complete genome
AFS88936		2012 Jun. 13	2012 Sep. 27	Human betacoronavirus 2c EMC/2012, complete genome
AGG22542	United Kingdom	2012 Sep. 19	2013 Feb. 27	Human betacoronavirus 2c England-Qatar/2012, complete genome
AHY21469	Jordan	2012	2014 May 4	Human betacoronavirus 2c Jordan-N3/2012 isolate MG167, complete genome
AGH58717	Jordan	2012 April	2013 Mar. 25	Human betacoronavirus 2c Jordan-N3/2012, complete genome
AGV08444	Saudi Arabia	2013 May 7	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Al-Hasa_12_2013, complete genome
AGV08546	Saudi Arabia	2013 May 11	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Al-Hasa_15_2013, complete genome
AGV08535	Saudi Arabia	2013 May 12	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Al-Hasa_16_2013, complete genome
AGV08558	Saudi Arabia	2013 May 15	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Al-Hasa_17_2013, complete genome
AGV08573	Saudi Arabia	2013 May 23	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Al-Hasa_18_2013, complete genome
AGV08480	Saudi Arabia	2013 May 23	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Al-Hasa_19_2013, complete genome
AGN70962	Saudi Arabia	2013 May 9	2013 Jun. 10	Middle East respiratory syndrome coronavirus isolate Al-Hasa_1_2013, complete genome
AGV08492	Saudi Arabia	2013 May 30	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Al-Hasa_21_2013, complete genome
AHI48517	Saudi Arabia	2013 May 2	2014 Feb. 6	Middle East respiratory syndrome coronavirus isolate Al-Hasa_25_2013, complete genome
AGN70951	Saudi Arabia	2013 Apr. 21	2013 Jun. 10	Middle East respiratory syndrome coronavirus isolate Al-Hasa_2_2013, complete genome
AGN70973	Saudi Arabia	2013 Apr. 22	2013 Jun. 10	Middle East respiratory syndrome coronavirus isolate Al-Hasa_3_2013, complete genome
AGN70929	Saudi Arabia	2013 May 1	2013 Jun. 10	Middle East respiratory syndrome coronavirus isolate Al-Hasa_4_2013, complete genome
AGV08408	Saudi Arabia	2012 Jun. 19	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Bisha_1_2012, complete genome
AGV08467	Saudi Arabia	2013 May 13	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Buraidah_1_2013, complete genome
AID50418	United Kingdom	2013 Feb. 10	2014 Jun. 18	Middle East respiratory syndrome coronavirus isolate England/2/2013, complete genome
AJD81451	United Kingdom	2013 Feb. 10	2015 Jan. 18	Middle East respiratory syndrome coronavirus isolate England/3/2013, complete genome
AJD81440	United Kingdom	2013 Feb. 13	2015 Jan. 18	Middle East respiratory syndrome coronavirus isolate England/4/2013, complete genome
AHB33326	France	2013 May 7	2013 Dec. 7	Middle East respiratory syndrome coronavirus isolate FRA/UAE, complete genome
AIZ48760	USA	2014 June	2014 Dec. 14	Middle East respiratory syndrome coronavirus isolate Florida/USA-2_Saudi Arabia_2014, complete genome
AGV08455	Saudi Arabia	2013 Jun. 4	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Hafr-Al-Batin_1_2013, complete genome
AHI48561	Saudi Arabia	2013 Aug. 5	2014 Feb. 6	Middle East respiratory syndrome coronavirus isolate Hafr-Al-Batin_2_2013, complete genome

TABLE 12-continued

Full-length Spike Glycoprotein Amino Acid Sequences (*Homo sapiens* strains)

GenBank Accession	Country	Collection Date	Release Date	Virus Name
AHI48539	Saudi Arabia	2013 Aug. 28	2014 Feb. 6	Middle East respiratory syndrome coronavirus isolate Hafr-Al-Batin_6_2013, complete genome
AIZ74417	France	2013 Apr. 26	2015 Mar. 10	Middle East respiratory syndrome coronavirus isolate Hu-France (UAE) - FRA1_1627-2013_BAL_Sanger, complete genome
AIZ74433	France	2013 May 7	2015 Mar. 10	Middle East respiratory syndrome coronavirus isolate Hu-France - FRA2_130569-2013_IS_HTS, complete genome
AIZ74439	France	2013 May 7	2015 Mar. 10	Middle East respiratory syndrome coronavirus isolate Hu-France - FRA2_130569-2013_InSpu_Sanger, complete genome
AIZ74450	France	2013 May 7	2015 Mar. 10	Middle East respiratory syndrome coronavirus isolate Hu-France - FRA2_130569-2013_Isolate_Sanger, complete genome
AKK52602	Saudi Arabia	2015 Feb. 10	2015 Jun. 8	Middle East respiratory syndrome coronavirus isolate Hu/Riyadh_KSA_2959_2015, complete genome
AKK52612	Saudi Arabia	2015 Mar. 1	2015 Jun. 8	Middle East respiratory syndrome coronavirus isolate Hu/Riyadh_KSA_4050_2015, complete genome
AHN10812	Saudi Arabia	2013 Nov. 6	2014 Mar. 24	Middle East respiratory syndrome coronavirus isolate Jeddah_1_2013, complete genome
AID55071	Saudi Arabia	2014 Apr. 21	2014 Nov. 12	Middle East respiratory syndrome coronavirus isolate Jeddah_C10306/KSA/2014-04-20, complete genome
AID55066	Saudi Arabia	2014	2014 Nov. 12	Middle East respiratory syndrome coronavirus isolate Jeddah_C7149/KSA/2014-04-05, complete genome
AID55067	Saudi Arabia	2014	2014 Nov. 12	Middle East respiratory syndrome coronavirus isolate Jeddah_C7569/KSA/2014-04-03, complete genome
AID55068	Saudi Arabia	2014 Apr. 7	2014 Nov. 12	Middle East respiratory syndrome coronavirus isolate Jeddah_C7770/KSA/2014-04-07, complete genome
AID55069	Saudi Arabia	2014 Apr. 12	2014 Nov. 12	Middle East respiratory syndrome coronavirus isolate Jeddah_C8826/KSA/2014-04-12, complete genome
AID55070	Saudi Arabia	2014 Apr. 14	2014 Nov. 12	Middle East respiratory syndrome coronavirus isolate Jeddah_C9055/KSA/2014-04-14, complete genome
AHE78108	Saudi Arabia	2013 Nov. 5	2014 May 1	Middle East respiratory syndrome coronavirus isolate MERS-CoV-Jeddah-human-1, complete genome
AKL59401	South Korea	2015 May 20	2015 Jun. 9	Middle East respiratory syndrome coronavirus isolate MERS-CoV/KOR/KNIH/002_05_2015, complete genome
ALD51904	Thailand	2015 Jun. 17	2015 Jul. 7	Middle East respiratory syndrome coronavirus isolate MERS-CoV/THA/CU/17_06_2015, complete genome
AID55072	Saudi Arabia	2014 Apr. 15	2014 Nov. 12	Middle East respiratory syndrome coronavirus isolate Makkah_C9355/KSA/Makkah/2014-04-15, complete genome
AHC74088	Qatar	2013 Oct. 13	2013 Dec. 23	Middle East respiratory syndrome coronavirus isolate Qatar3, complete genome

TABLE 12-continued

Full-length Spike Glycoprotein Amino Acid Sequences (*Homo sapiens* strains)

GenBank Accession	Country	Collection Date	Release Date	Virus Name
AHC74098	Qatar	2013 Oct. 17	2013 Dec. 23	Middle East respiratory syndrome coronavirus isolate Qatar4, complete genome
AHI48572	Saudi Arabia	2013 Aug. 15	2014 Feb. 6	Middle East respiratory syndrome coronavirus isolate Riyadh_14_2013, complete genome
AGV08379	Saudi Arabia	2012 Oct. 23	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Riyadh_1_2012, complete genome
AID55073	Saudi Arabia	2014 Apr. 22	2014 Nov. 12	Middle East respiratory syndrome coronavirus isolate Riyadh_2014KSA_683/KSA/2014, complete genome
AGV08584	Saudi Arabia	2012 Oct. 30	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Riyadh_2_2012, complete genome
AGV08390	Saudi Arabia	2013 Feb. 5	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Riyadh_3_2013, complete genome
AHI48605	Saudi Arabia	2013 Mar. 1	2014 Feb. 6	Middle East respiratory syndrome coronavirus isolate Riyadh_4_2013, complete genome
AHI48583	Saudi Arabia	2013 Jul. 2	2014 Feb. 6	Middle East respiratory syndrome coronavirus isolate Riyadh_5_2013, complete genome
AHI48528	Saudi Arabia	2013 Jul. 17	2014 Feb. 6	Middle East respiratory syndrome coronavirus isolate Riyadh_9_2013, complete genome
AHI48594	Saudi Arabia	2013 Jun. 12	2014 Feb. 6	Middle East respiratory syndrome coronavirus isolate Taif_1_2013, complete genome
AHI48550	Saudi Arabia	2013 Jun. 12	2014 Feb. 6	Middle East respiratory syndrome coronavirus isolate Wadi-Ad-Dawasir_1_2013, complete genome
AIY60558	United Arab Emirates	2014 Mar. 7	2014 Dec. 6	Middle East respiratory syndrome coronavirus strain Abu Dhabi/Gayathi_UAE_2_2014, complete genome
AIY60538	United Arab Emirates	2014 Apr. 10	2014 Dec. 6	Middle East respiratory syndrome coronavirus strain Abu Dhabi_UAE_16_2014, complete genome
AIY60528	United Arab Emirates	2014 Apr. 10	2014 Dec. 6	Middle East respiratory syndrome coronavirus strain Abu Dhabi_UAE_18_2014, complete genome
AIY60588	United Arab Emirates	2014 Apr. 13	2014 Dec. 6	Middle East respiratory syndrome coronavirus strain Abu Dhabi_UAE_26_2014, complete genome
AIY60548	United Arab Emirates	2014 Apr. 19	2014 Dec. 6	Middle East respiratory syndrome coronavirus strain Abu Dhabi_UAE_30_2014, complete genome
AIY60568	United Arab Emirates	2014 Apr. 17	2014 Dec. 6	Middle East respiratory syndrome coronavirus strain Abu Dhabi_UAE_33_2014, complete genome
AIY60518	United Arab Emirates	2014 Apr. 7	2014 Dec. 6	Middle East respiratory syndrome coronavirus strain Abu Dhabi_UAE_8_2014, complete genome
AIY60578	United Arab Emirates	2013 Nov. 15	2014 Dec. 6	Middle East respiratory syndrome coronavirus strain Abu Dhabi_UAE_9_2013, complete genome
AKJ80137	China	2015 May 27	2015 Jun. 5	Middle East respiratory syndrome coronavirus strain ChinaGD01, complete genome
AHZ64057	USA	2014 May 10	2014 May 14	Middle East respiratory syndrome coronavirus strain Florida/USA-2_Saudi Arabia_2014, complete genome
AKM76229	Oman	2013 Oct. 28	2015 Jun. 23	Middle East respiratory syndrome coronavirus strain

TABLE 12-continued

Full-length Spike Glycoprotein Amino Acid Sequences (*Homo sapiens* strains)

GenBank Accession	Country	Collection Date	Release Date	Virus Name
				Hu/Oman_2285_2013, complete genome
AKM76239	Oman	2013 Dec. 28	2015 Jun. 23	Middle East respiratory syndrome coronavirus strain Hu/Oman_2874_2013, complete genome
AKI29284	Saudi Arabia	2015 Jan. 6	2015 May 27	Middle East respiratory syndrome coronavirus strain Hu/Riyadh-KSA-2049/2015, complete genome
AKI29265	Saudi Arabia	2015 Jan. 21	2015 May 27	Middle East respiratory syndrome coronavirus strain Hu/Riyadh-KSA-2343/2015, complete genome
AKI29255	Saudi Arabia	2015 Jan. 21	2015 May 27	Middle East respiratory syndrome coronavirus strain Hu/Riyadh-KSA-2345/2015, complete genome
AKI29275	Saudi Arabia	2015 Jan. 26	2015 May 27	Middle East respiratory syndrome coronavirus strain Hu/Riyadh-KSA-2466/2015, complete genome
AKK52582	Saudi Arabia	2015 Feb. 10	2015 Jun. 8	Middle East respiratory syndrome coronavirus strain Hu/Riyadh_KSA_2959_2015, complete genome
AKK52592	Saudi Arabia	2015 Mar. 1	2015 Jun. 8	Middle East respiratory syndrome coronavirus strain Hu/Riyadh_KSA_4050_2015, complete genome
AHZ58501	USA	2014 Apr. 30	2014 May 13	Middle East respiratory syndrome coronavirus strain Indiana/USA-1_Saudi Arabia_2014, complete genome
AGN52936	United Arab Emirates	2013	2013 Jun. 10	Middle East respiratory syndrome coronavirus, complete genome

TABLE 13

MeV Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
GC_F_MEASLES_B3.1 Sequence, NT (5' UTR, ORF, 3' UTR) Sequence Length: 1864	TCAAGCTTTTGGACCCTCGTACAGAAGCTAATACGACT CACTATAGGGAAATAAGAGAGAAAAGAAGAGTAAGAA GAAATATAAGAGCCACCATGGGTCTCAAGGTGAACGTC TCTGCCGTATTCATGGCAGTACTGTTAACTCTCCAAACA CCCGCCGGTCAAATTCATTGGGGCAATCTCTCTAAGAT AGGGGTAGTAGGAATAGGAAGTGCAAGCTACAAAGTT ATGACTCGTTCCAGCCATCAATCATTAGTCATAAAATT AATGCCCAATATAACTCTCCTCAATAACTGCACGAGGG TAGAGATTGCAGAATACAGGAGACTACTAAGAACAGTT TTGGAACCAATTAGGGATGCACTTAATGCAATGACCCA GAACATAAGGCCGGTTCAGAGCGTAGCTTCAAGTAGGA GACACAAGAGATTTGCGGGAGTAGTCCTGGCAGGTGCG GCCCTAGGTGTTGCCACAGCTGCTCAGATAACAGCCGG CATTGCACTTCACCGGTCCATGCTGAACTCTCAGGCCAT CGACAATCTGAGAGCGAGCCTGGAAACTACTAATCAGG CAATTGAGGCAATCAGACAAGCAGGGCAGGAGATGAT ATTGGCTGTTCAGGGTGTCCAAGACTACATCAATAATG AGCTGATACCGTCTATGAACCAGCTATCTTGTGATCTA ATCGGTCAGAAGCTCGGGCTCAAATTGCTTAGATACTA TACAGAAATCCTGTCATTATTTGGCCCCAGCCTACGGG ACCCCATATCTGCGGAGATATCTATCCAGGCTTTGAGTT ATGCACTTGGAGGAGATATCAATAAGGTGTTAGAAAAG CTCGGATACAGTGGAGGCGATTTACTAGGCATCTTAGA GAGCAGAGGAATAAAGGCTCGGATAACTCACGTCGAC ACAGAGTCCTACTTCATAGTCCTCAGTATAGCCTATCCG ACGCTGTCCGAGATTAAGGGGGTGATTGTCCACCGGCT AGAGGGGGTCTCGTACAACATAGGCTCTCAAGAGTGGT ATACCACTGTGCCCAAGTATGTTGCAACCCAAGGGTAC CTTATCTCGAATTTTGATGAGTCATCATGTACTTTCATG CCAGAGGGGACTGTGTGCAGCCAAAATGCCTTGTACCC GATGAGTCCTCTGCTCCAAGAATGCCTCCGGGGGTCCA	35

TABLE 13-continued

MeV Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
	CCAAGTCCTGTGCTCGTACACTCGTATCCGGGTCTTTTG	
	GGAACCGGTTCATTTTATCACAAGGGAACCTAATAGCC	
	AATTGTGCATCAATTCTTTGTAAGTGTTACACAACAGGT	
	ACGATTATTAATCAAGACCCTGACAAGATCCTAACATA	
	CATTGCTGCCGATCGCTGCCCGGTAGTCGAGGTGAACG	
	GCGTGACCATCCAAGTCGGGAGCAGGAGGTATCCAGA	
	CGCTGTGTACTTGCACAGAATTGACCTCGGTCCTCCCAT	
	ATCATTGGAGAGGTTGGACGTAGGGACAAATCTGGGG	
	AATGCAATTGCCAAATTGGAGGATGCCAAGGAATTGTT	
	GGAATCATCGGACCAGATATTGAGAAGTATGAAAGGTT	
	TATCGAGCACTAGCATAGTCTACATCCTGATTGCAGTG	
	TGTCTTGGAGGGTTGATAGGGATCCCCACTTTAATATGT	
	TGCTGCAGGGGGCGTTGTAACAAAAAGGGAGAACAAG	
	TTGGTATGTCAAGACCAGGCCTAAAGCCTGACCTTACA	
	GGAACATCAAAATCCTATGTAAGATCGCTTTGATGATA	
	ATAGGCTGGAGCCTCGGTGGCCAAGCTTCTTGCCCCTT	
	GGGCCTCCCCCCAGCCCCTCCTCCCCTTCCTGCACCCGT	
	ACCCCCGTGGTCTTTGAATAAAGTCTGAGTGGGCGGC	
GC_F_MEASLES_B3.1 ORF Sequence, NT	ATGGGTCTCAAGGTGAACGTCTCTGCCGTATTCATGGC	36
	AGTACTGTTAACTCTCCAAACACCCGCCGGTCAAATTC	
	ATTGGGGCAATCTCTCTAAGATAGGGGTAGTAGGAATA	
	GGAAGTGCAAGCTACAAAGTTATGACTCGTTCCAGCCA	
	TCAATCATTAGTCATAAAATTAATGCCCAATATAACTCT	
	CCTCAATAACTGCACGAGGGTAGAGATTGCAGAATACA	
	GGAGACTACTAAGAACAGTTTTGGAACCAATTAGGGAT	
	GCACTTAATGCAATGACCCAGAACATAAGGCCGGTTCA	
	GAGCGTAGCTTCAAGTAGGAGACACAAGAGATTTGCG	
	GGAGTAGTCCTGGCAGGTGCGGCCCTAGGTGTTGCCAC	
	AGCTGCTCAGATAACAGCCGGCATTGCACTTCACCGGT	
	CCATGCTGAACTCTCAGGCCATCGACAATCTGAGAGCG	
	AGCCTGGAAACTACTAATCAGGCAATTGAGGCAATCAG	
	ACAAGCAGGGCAGGAGATGATATTGGCTGTTCAGGGTG	
	TCCAAGACTACATCAATAATGAGCTGATACCGTCTATG	
	AACCAGCTATCTTGTGATCTAATCGGTCAGAAGCTCGG	
	GCTCAAATTGCTTAGATACTATACAGAAATCCTGTCATT	
	ATTTGGCCCCAGCCTACGGGACCCCATATCTGCGGAGA	
	TATCTATCCAGGCTTTGAGTTATGCACTTGGAGGAGAT	
	ATCAATAAGGTGTTAGAAAAGCTCGGATACAGTGGAG	
	GCGATTTACTAGGCATCTTAGAGAGCAGAGGAATAAAG	
	GCTCGGATAACTCACGTCGACACAGAGTCCTACTTCAT	
	AGTCCTCAGTATAGCCTATCCGACGCTGTCCGAGATTA	
	AGGGGGTGATTGTCCACCGGCTAGAGGGGGTCTCGTAC	
	AACATAGGCTCTCAAGAGTGGTATACCACTGTGCCCAA	
	GTATGTTGCAACCCAAGGGTACCTTATCTCGAATTTTGA	
	TGAGTCATCATGTACTTTCATGCCAGAGGGGACTGTGT	
	GCAGCCAAAATGCCTTGTACCCGATGAGTCCTCTGCTC	
	CAAGAATGCCTCCGGGGGTCCACCAAGTCCTGTGCTCG	
	TACACTCGTATCCGGGTCTTTTGGGAACCGGTTCATTTT	
	ATCACAAGGGAACCTAATAGCCAATTGTGCATCAATTC	
	TTTGTAAGTGTTACACAACAGGTACGATTATTAATCAA	
	GACCCTGACAAGATCCTAACATACATTGCTGCCGATCG	
	CTGCCCGGTAGTCGAGGTGAACGGCGTGACCATCCAAG	
	TCGGGAGCAGGAGGTATCCAGACGCTGTGTACTTGCAC	
	AGAATTGACCTCGGTCCTCCCATATCATTGGAGAGGTT	
	GGACGTAGGGACAAATCTGGGGAATGCAATTGCCAAA	
	TTGGAGGATGCCAAGGAATTGTTGGAATCATCGGACCA	
	GATATTGAGAAGTATGAAAGGTTTATCGAGCACTAGCA	
	TAGTCTACATCCTGATTGCAGTGTGTCTTGGAGGGTTGA	
	TAGGGATCCCCACTTTAATATGTTGCTGCAGGGGGCGT	
	TGTAACAAAAAGGGAGAACAAGTTGGTATGTCAAGAC	
	CAGGCCTAAAGCCTGACCTTACAGGAACATCAAAATCC	
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GC_F_MEASLES_B3.1 mRNA Sequence (assumes T100 tail) mRNA Sequence Length: 1925	G*GGGAAATAAGAGAGAAAAGAAGAGTAAGAAGAAAT	37
	ATAAGAGCCACCATGGGTCTCAAGGTGAACGTCTCTGC	
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	CCGGTCAAATTCATTGGGGCAATCTCTCTAAGATAGGG	
	GTAGTAGGAATAGGAAGTGCAAGCTACAAAGTTATGA	
	CTCGTTCCAGCCATCAATCATTAGTCATAAAATTAATGC	
	CCAATATAACTCTCCTCAATAACTGCACGAGGGTAGAG	
	ATTGCAGAATACAGGAGACTACTAAGAACAGTTTTGGA	
	ACCAATTAGGGATGCACTTAATGCAATGACCCAGAACA	
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TABLE 13-continued

MeV Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
	AGGTGTTGCCACAGCTGCTCAGATAACAGCCGGCATTG	
	CACTTCACCGGTCCATGCTGAACTCTCAGGCCATCGAC	
	AATCTGAGAGCGAGCCTGGAAACTACTAATCAGGCAAT	
	TGAGGCAATCAGACAAGCAGGGCAGGAGATGATATTG	
	GCTGTTCAGGGTGTCCAAGACTACATCAATAATGAGCT	
	GATACCGTCTATGAACCAGCTATCTTGTGATCTAATCG	
	GTCAGAAGCTCGGGCTCAAATTGCTTAGATACTATACA	
	GAAATCCTGTCATTATTTGGCCCCAGCCTACGGGACCC	
	CATATCTGCGGAGATATCTATCCAGGCTTTGAGTTATGC	
	ACTTGGAGGAGATATCAATAAGGTGTTAGAAAAGCTCG	
	GATACAGTGGAGGCGATTTACTAGGCATCTTAGAGAGC	
	AGAGGAATAAAGGCTCGGATAACTCACGTCGACACAG	
	AGTCCTACTTCATAGTCCTCAGTATAGCCTATCCGACGC	
	TGTCCGAGATTAAGGGGGTGATTGTCCACCGGCTAGAG	
	GGGGTCTCGTACAACATAGGCTCTCAAGAGTGGTATAC	
	CACTGTGCCCAAGTATGTTGCAACCCAAGGGTACCTTA	
	TCTCGAATTTTGATGAGTCATCATGTACTTTCATGCCAG	
	AGGGGACTGTGTGCAGCCAAAATGCCTTGTACCCGATG	
	AGTCCTCTGCTCCAAGAATGCCTCCGGGGGTCCACCAA	
	GTCCTGTGCTCGTACACTCGTATCCGGGTCTTTTGGGAA	
	CCGGTTCATTTTATCACAAGGGAACCTAATAGCCAATT	
	GTGCATCAATTCTTTGTAAGTGTTACACAACAGGTACG	
	ATTATTAATCAAGACCCTGACAAGATCCTAACATACAT	
	TGCTGCCGATCGCTGCCCGGTAGTCGAGGTGAACGGCG	
	TGACCATCCAAGTCGGGAGCAGGAGGTATCCAGACGCT	
	GTGTACTTGCACAGAATTGACCTCGGTCCTCCCATATCA	
	TTGGAGAGGTTGGACGTAGGGACAAATCTGGGGAATG	
	CAATTGCCAAATTGGAGGATGCCAAGGAATTGTTGGAA	
	TCATCGGACCAGATATTGAGAAGTATGAAAGGTTTATC	
	GAGCACTAGCATAGTCTACATCCTGATTGCAGTGTGTC	
	TTGGAGGGTTGATAGGGATCCCCACTTTAATATGTTGCT	
	GCAGGGGGCGTTGTAACAAAAAGGGAGAACAAGTTGG	
	TATGTCAAGACCAGGCCTAAAGCCTGACCTTACAGGAA	
	CATCAAAATCCTATGTAAGATCGCTTTGATGATAATAG	
	GCTGGAGCCTCGGTGGCCAAGCTTCTTGCCCCTTGGGC	
	CTCCCCCCAGCCCCTCCTCCCCTTCCTGCACCCGTACCC	
	CCGTGGTCTTTGAATAAAGTCTGAGTGGGCGGCAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAATCTAG	
GC_F_MEASLES_D8 Sequence, NT (5' UTR, ORF, 3' UTR) Sequence Length: 1864	TCAAGCTTTTGGACCCTCGTACAGAAGCTAATACGACT CACTATAGGGAAATAAGAGAGAAAAGAAGAGTAAGAA GAAATATAAGAGCCACCATGGGTCTCAAGGTGAACGTC TCTGTCATATTCATGGCAGTACTGTTAACTCTTCAAACA CCCACCGGTCAAATCCATTGGGGCAATCTCTCTAAGAT AGGGGTGGTAGGGGTAGGAAGTGCAAGCTACAAAGTT ATGACTCGTTCCAGCCATCAATCATTAGTCATAAAGTT AATGCCCAATATAACTCTCCTCAACAATTGCACGAGGG TAGGGATTGCAGAATACAGGAGACTACTGAGAACAGTT CTGGAACCAATTAGAGATGCACTTAATGCAATGACCCA GAATATAAGACCGGTTCAGAGTGTAGCTTCAAGTAGGA GACACAAGAGATTTGCGGGAGTTGTCCTGGCAGGTGCG GCCCTAGGCGTTGCCACAGCTGCTCAAATAACAGCCGG TATTGCACTTCACCAGTCCATGCTGAACTCTCAAGCCAT CGACAATCTGAGAGCGAGCCTAGAAACTACTAATCAGG CAATTGAGGCAATCAGACAAGCAGGGCAGGAGATGAT ATTGGCTGTTCAGGGTGTCCAAGACTACATCAATAATG AGCTGATACCGTCTATGAATCAACTATCTTGTGATTTAA TCGGCCAGAAGCTAGGGCTCAAATTGCTCAGATACTAT ACAGAAATCCTGTCATTATTTGGCCCCAGCTTACGGGA CCCCATATCTGCGGAGATATCTATCCAGGCTTTGAGCT ATGCGCTTGGAGGAGATATCAATAAGGTGTTGGAAAAG CTCGGATACAGTGGAGGTGATCTACTGGGCATCTTAGA GAGCAGAGGAATAAAGGCCCGGATAACTCACGTCGAC ACAGAGTCCTACTTCATTGTACTCAGTATAGCCTATCCG ACGCTATCCGAGATTAAGGGGGTGATTGTCCACCGGCT AGAGGGGGTCTCGTACAACATAGGCTCTCAAGAGTGGT ATACCACTGTGCCCAAGTATGTTGCAACCCAAGGGTAC CTTATCTCGAATTTTGATGAGTCATCATGCACTTTCATG CCAGAGGGGACTGTGTGCAGCCAGAATGCCTTGTACCC GATGAGTCCTCTGCTCCAAGAATGCCTCCGGGGGTCCA CTAAGTCCTGTGCTCGTACACTCGTATCCGGGTCTTTCG GGAACCGGTTCATTTTATCACAGGGGAACCTAATAGCC AATTGTGCATCAATCCTTTGCAAGTGTTACACAACAGG	38

TABLE 13-continued

MeV Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
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	ACATTGCTGCCGATCACTGCCCGGTGGTCGAGGTGAAT	
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	ACGCTGTGTACTTGCACAGGATTGACCTCGGTCCTCCC	
	ATATCTTTGGAGAGGTTGGACGTAGGGACAAATCTGGG	
	GAATGCAATTGCTAAGTTGGAGGATGCCAAGGAATTGT	
	TGGAGTCATCGGACCAGATATTGAGGAGTATGAAAGGT	
	TTATCGAGCACTAGTATAGTTTACATCCTGATTGCAGTG	
	TGTCTTGGAGGATTGATAGGGATCCCCGCTTTAATATGT	
	TGCTGCAGGGGGCGTTGTAACAAGAAGGGAGAACAAG	
	TTGGTATGTCAAGACCAGGCCTAAAGCCTGATCTTACA	
	GGAACATCAAAATCCTATGTAAGGTCACTCTGATGATA	
	ATAGGCTGGAGCCTCGGTGGCCAAGCTTCTTGCCCCTT	
	GGGCCTCCCCCCAGCCCCTCCTCCCCTTCCTGCACCCGT	
	ACCCCCGTGGTCTTTGAATAAAGTCTGAGTGGGCGGC	
GC_F_MEASLES_D8 ORF Sequence, NT	ATGGGTCTCAAGGTGAACGTCTCTGTCATATTCATGGC	39
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	ATTGGGGCAATCTCTCTAAGATAGGGGTGGTAGGGGTA	
	GGAAGTGCAAGCTACAAAGTTATGACTCGTTCCAGCCA	
	TCAATCATTAGTCATAAAGTTAATGCCCAATATAACTCT	
	CCTCAACAATTGCACGAGGGTAGGGATTGCAGAATACA	
	GGAGACTACTGAGAACAGTTCTGGAACCAATTAGAGAT	
	GCACTTAATGCAATGACCCAGAATATAAGACCGGTTCA	
	GAGTGTAGCTTCAAGTAGGAGACACAAGAGATTTGCGG	
	GAGTTGTCCTGGCAGGTGCGGCCCTAGGCGTTGCCACA	
	GCTGCTCAAATAACAGCCGGTATTGCACTTCACCAGTC	
	CATGCTGAACTCTCAAGCCATCGACAATCTGAGAGCGA	
	GCCTAGAAACTACTAATCAGGCAATTGAGGCAATCAGA	
	CAAGCAGGGCAGGAGATGATATTGGCTGTTCAGGGTGT	
	CCAAGACTACATCAATAATGAGCTGATACCGTCTATGA	
	ATCAACTATCTTGTGATTTAATCGGCCAGAAGCTAGGG	
	CTCAAATTGCTCAGATACTATACAGAAATCCTGTCATT	
	ATTTGGCCCCAGCTTACGGGACCCCATATCTGCGGAGA	
	TATCTATCCAGGCTTTGAGCTATGCGCTTGGAGGAGAT	
	ATCAATAAGGTGTTGGAAAAGCTCGGATACAGTGGAG	
	GTGATCTACTGGGCATCTTAGAGAGCAGAGGAATAAAG	
	GCCCGGATAACTCACGTCGACACAGAGTCCTACTTCAT	
	TGTACTCAGTATAGCCTATCCGACGCTATCCGAGATTA	
	AGGGGGTGATTGTCCACCGGCTAGAGGGGGTCTCGTAC	
	AACATAGGCTCTCAAGAGTGGTATACCACTGTGCCCAA	
	GTATGTTGCAACCCAAGGGTACCTTATCTCGAATTTTGA	
	TGAGTCATCATGCACTTTCATGCCAGAGGGGACTGTGT	
	GCAGCCAGAATGCCTTGTACCCGATGAGTCCTCTGCTC	
	CAAGAATGCCTCCGGGGGTCCACTAAGTCCTGTGCTCG	
	TACACTCGTATCCGGGTCTTTCGGGAACCGGTTCATTTT	
	ATCACAGGGGAACCTAATAGCCAATTGTGCATCAATCC	
	TTTGCAAGTGTTACACAACAGGAACAATCATTAATCAA	
	GACCCTGACAAGATCCTAACATACATTGCTGCCGATCA	
	CTGCCCGGTGGTCGAGGTGAATGGCGTGACCATCCAAG	
	TCGGGAGCAGGAGGTATCCGGACGCTGTGTACTTGCAC	
	AGGATTGACCTCGGTCCTCCCATATCTTTGGAGAGGTT	
	GGACGTAGGGACAAATCTGGGGAATGCAATTGCTAAGT	
	TGGAGGATGCCAAGGAATTGTTGGAGTCATCGGACCAG	
	ATATTGAGGAGTATGAAAGGTTTATCGAGCACTAGTAT	
	AGTTTACATCCTGATTGCAGTGTGTCTTGGAGGATTGAT	
	AGGGATCCCCGCTTTAATATGTTGCTGCAGGGGGCGTT	
	GTAACAAGAAGGGAGAACAAGTTGGTATGTCAAGACC	
	AGGCCTAAAGCCTGATCTTACAGGAACATCAAAATCCT	
	ATGTAAGGTCACTCTGA	
GC_F_MEASLES_D8 mRNA Sequence (assumes T100 tail) Sequence Length: 1925	G*GGGAAATAAGAGAGAAAAGAAGAGTAAGAAGAAAT	40
	ATAAGAGCCACCATGGGTCTCAAGGTGAACGTCTCTGT	
	CATATTCATGGCAGTACTGTTAACTCTTCAAACACCCAC	
	CGGTCAAATCCATTGGGGCAATCTCTCTAAGATAGGGG	
	TGGTAGGGGTAGGAAGTGCAAGCTACAAAGTTATGACT	
	CGTTCCAGCCATCAATCATTAGTCATAAAGTTAATGCC	
	CAATATAACTCTCCTCAACAATTGCACGAGGGTAGGGA	
	TTGCAGAATACAGGAGACTACTGAGAACAGTTCTGGAA	
	CCAATTAGAGATGCACTTAATGCAATGACCCAGAATAT	
	AAGACCGGTTCAGAGTGTAGCTTCAAGTAGGAGACACA	
	AGAGATTTGCGGGAGTTGTCCTGGCAGGTGCGGCCCTA	
	GGCGTTGCCACAGCTGCTCAAATAACAGCCGGTATTGC	
	ACTTCACCAGTCCATGCTGAACTCTCAAGCCATCGACA	
	ATCTGAGAGCGAGCCTAGAAACTACTAATCAGGCAATT	

TABLE 13-continued

MeV Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
	GAGGCAATCAGACAAGCAGGGCAGGAGATGATATTGG	
	CTGTTCAGGGTGTCCAAGACTACATCAATAATGAGCTG	
	ATACCGTCTATGAATCAACTATCTTGTGATTTAATCGGC	
	CAGAAGCTAGGGCTCAAATTGCTCAGATACTATACAGA	
	AATCCTGTCATTATTTGGCCCCAGCTTACGGGACCCCAT	
	ATCTGCGGAGATATCTATCCAGGCTTTGAGCTATGCGC	
	TTGGAGGAGATATCAATAAGGTGTTGGAAAAGCTCGGA	
	TACAGTGGAGGTGATCTACTGGGCATCTTAGAGAGCAG	
	AGGAATAAAGGCCCGGATAACTCACGTCGACACAGAG	
	TCCTACTTCATTGTACTCAGTATAGCCTATCCGACGCTA	
	TCCGAGATTAAGGGGGTGATTGTCCACCGGCTAGAGGG	
	GGTCTCGTACAACATAGGCTCTCAAGAGTGGTATACCA	
	CTGTGCCCAAGTATGTTGCAACCCAAGGGTACCTTATC	
	TCGAATTTTGATGAGTCATCATGCACTTTCATGCCAGAG	
	GGGACTGTGTGCAGCCAGAATGCCTTGTACCCGATGAG	
	TCCTCTGCTCCAAGAATGCCTCCGGGGGTCCACTAAGT	
	CCTGTGCTCGTACACTCGTATCCGGGTCTTTCGGGAACC	
	GGTTCATTTTATCACAGGGGAACCTAATAGCCAATTGT	
	GCATCAATCCTTTGCAAGTGTTACACAACAGGAACAAT	
	CATTAATCAAGACCCTGACAAGATCCTAACATACATTG	
	CTGCCGATCACTGCCCGGTGGTCGAGGTGAATGGCGTG	
	ACCATCCAAGTCGGGAGCAGGAGGTATCCGGACGCTGT	
	GTACTTGCACAGGATTGACCTCGGTCCTCCCATATCTTT	
	GGAGAGGTTGGACGTAGGGACAAATCTGGGGAATGCA	
	ATTGCTAAGTTGGAGGATGCCAAGGAATTGTTGGAGTC	
	ATCGGACCAGATATTGAGGAGTATGAAAGGTTTATCGA	
	GCACTAGTATAGTTTACATCCTGATTGCAGTGTGTCTTG	
	GAGGATTGATAGGGATCCCCGCTTTAATATGTTGCTGC	
	AGGGGGCGTTGTAACAAGAAGGGAGAACAAGTTGGTA	
	TGTCAAGACCAGGCCTAAAGCCTGATCTTACAGGAACA	
	TCAAAATCCTATGTAAGGTCACTCTGATGATAATAGGC	
	TGGAGCCTCGGTGGCCAAGCTTCTTGCCCCTTGGGCCTC	
	CCCCCAGCCCCTCCTCCCCTTCCTGCACCCGTACCCCCG	
	TGGTCTTTGAATAAAGTCTGAGTGGGCGGCAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAATCTAG	
GC_H_MEASLES_B3 Sequence, NT (5' UTR, ORF, 3' UTR) Sequence Length: 2065	TCAAGCTTTTGGACCCTCGTACAGAAGCTAATACGACT CACTATAGGGAAATAAGAGAGAAAAGAAGAGTAAGAA GAAATATAAGAGCCACCATGTCACCGCAACGAGACCG GATAAATGCCTTCTACAAAGATAACCCTTATCCCAAGG GAAGTAGGATAGTTATTAACAGAGAACATCTTATGATT GACAGACCCTATGTTCTGCTGGCTGTTCTGTTCGTCATG TTTCTGAGCTTGATCGGATTGCTGGCAATTGCAGGCATT AGACTTCATCGGGCAGCCATCTACACCGCGGAGATCCA TAAAAGCCTCAGTACCAATCTGGATGTGACTAACTCCA TCGAGCATCAGGTCAAGGACGTGCTGACACCACTCTTT AAAATCATCGGGGATGAAGTGGGCCTGAGAACACCTC AGAGATTCACTGACCTAGTGAAATTCATCTCGGACAAG ATTAAATTCCTTAATCCGGATAGGGAGTACGACTTCAG AGATCTCACTTGGTGCATCAACCCGCCAGAGAGGATCA AACTAGATTATGATCAATACTGTGCAGATGTGGCTGCT GAAGAGCTCATGAATGCATTGGTGAACTCAACTCTACT GGAGACCAGAACAACCACTCAGTTCCTAGCTGTCTCAA AGGGAAACTGCTCAGGGCCCACTACAATCAGAGGTCA ATTCTCAAACATGTCGCTGTCCTTGTTGGACTTGTACTT AGGTCGAGGTTACAATGTGTCATCTATAGTCACTATGA CATCCCAGGGAATGTATGGGGGAACCTACCTAGTTGAA AAGCCTAATCTGAACAGCAAAGGGTCAGAGTTGTCACA ACTGAGCATGTACCGAGTGTTTGAAGTAGGTGTGATCA GAAACCCGGGTTTGGGGGCTCCGGTGTTCCATATGACA AACTATTTTGAGCAACCAGTCAGTAATGGTCTCGGCAA CTGTATGGTGGCTTTGGGGGAGCTCAAACTCGCAGCCC TTTGTCACGGGGACGATTCTATCATAATTCCCTATCAGG GATCAGGGAAAGGTGTCAGCTTCCAGCTCGTCAAGCTG GGTGTCTGGAAATCCCCAACCGACATGCAATCCTGGGT CCCCTTATCAACGGATGATCCAGTGGTAGACAGGCTTT ACCTCTCATCTCACAGAGGTGTCATCGCTGACAATCAA GCAAAATGGGCTGTCCCGACAACACGAACAGATGACA AGTTGCGAATGGAGACATGCTTCCAGCAGGCGTGTAAA GGTAAAATCCAAGCACTCTGCGAGAATCCCGAGTGGGT ACCATTGAAGGATAACAGGATTCCTTCATACGGGGTCC TGTCTGTTGATCTGAGTCTGACGGTTGAGCTTAAAATCA AAATTGCTTCGGGATTCGGGCCATTGATCACACACGGC	41

TABLE 13-continued

MeV Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
	TCAGGGATGGACCTATACAAATCCAACTGCAACAATGT GTATTGGCTGACTATTCCGCCAATGAGAAATCTAGCCT TAGGCGTAATCAACACATTGGAGTGGATACCGAGATTC AAGGTTAGTCCCAACCTCTTCACTGTCCCAATTAAGGA AGCAGGCGAAGACTGCCATGCCCCAACATACCTACCTG CGGAGGTGGACGGTGATGTCAAACTCAGTTCCAACCTG GTGATTCTACCTGGTCAAGATCTCCAATATGTTTTGGCA ACCTACGATACCTCCAGGGTTGAGCATGCTGTGGTTTA TTACGTTTACAGCCCAAGCCGCTCATTTTCTTACTTTTA TCCTTTTAGGTTGCCTATAAAGGGGGTCCCAATCGAAC TACAAGTGGAATGCTTCACATGGGATCAAAAACTCTGG TGCCGTCACTTCTGTGTGCTTGCGGACTCAGAATCCGGT GGACTTATCACTCACTCTGGGATGGTGGGCATGGGAGT CAGCTGCACAGCTACCCGGGAAGATGGAACCAATCGC AGATAATGATAATAGGCTGGAGCCTCGGTGGCCAAGCT TCTTGCCCCTTGGGCCTCCCCCCAGCCCCTCCTCCCCTT CCTGCACCCGTACCCCCGTGGTCTTTGAATAAAGTCTG AGTGGGCGGC	
GC_H_MEASLES_B3 ORF Sequence, NT	ATGTCACCGCAACGAGACCGGATAAATGCCTTCTACAA AGATAACCCTTATCCCAAGGGAAGTAGGATAGTTATTA ACAGAGAACATCTTATGATTGACAGACCCTATGTTCTG CTGGCTGTTCTGTTCGTCATGTTTCTGAGCTTGATCGGA TTGCTGGCAATTGCAGGCATTAGACTTCATCGGGCAGC CATCTACACCGCGGAGATCCATAAAAGCCTCAGTACCA ATCTGGATGTGACTAACTCCATCGAGCATCAGGTCAAG GACGTGCTGACACCACTCTTTAAAATCATCGGGGATGA AGTGGGCCTGAGAACACCTCAGAGATTCACTGACCTAG TGAAATTCATCTCGGACAAGATTAAATTCCTTAATCCG GATAGGGAGTACGACTTCAGAGATCTCACTTGGTGCAT CAACCCGCCAGAGAGGATCAAACTAGATTATGATCAAT ACTGTGCAGATGTGGCTGCTGAAGAGCTCATGAATGCA TTGGTGAACTCAACTCTACTGGAGACCAGAACAACCAC TCAGTTCCTAGCTGTCTCAAAGGGAAACTGCTCAGGGC CCACTACAATCAGAGGTCAATTCTCAAACATGTCGCTG TCCTTGTTGGACTTGTACTTAGGTCGAGGTTACAATGTG TCATCTATAGTCACTATGACATCCCAGGGAATGTATGG GGGAACCTACCTAGTTGAAAAGCCTAATCTGAACAGCA AAGGGTCAGAGTTGTCACAACTGAGCATGTACCGAGTG TTTGAAGTAGGTGTGATCAGAAACCCGGGTTTGGGGGC TCCGGTGTTCCATATGACAAACTATTTTGAGCAACCAG TCAGTAATGGTCTCGGCAACTGTATGGTGGCTTTGGGG GAGCTCAAACTCGCAGCCCTTTGTCACGGGGACGATTC TATCATAATTCCCTATCAGGGATCAGGGAAAGGTGTCA GCTTCCAGCTCGTCAAGCTGGGTGTCTGGAAATCCCCA ACCGACATGCAATCCTGGGTCCCCTTATCAACGGATGA TCCAGTGGTAGACAGGCTTTACCTCTCATCTCACAGAG GTGTCATCGCTGACAATCAAGCAAAATGGGCTGTCCCG ACAACACGAACAGATGACAAGTTGCGAATGGAGACAT GCTTCCAGCAGGCGTGTAAAGGTAAAATCCAAGCACTC TGCGAGAATCCCGAGTGGGTACCATTGAAGGATAACAG GATTCCTTCATACGGGGTCCTGTCTGTTGATCTGAGTCT GACGGTTGAGCTTAAAATCAAAATTGCTTCGGGATTCG GGCCATTGATCACACACGGCTCAGGGATGGACCTATAC AAATCCAACTGCAACAATGTGTATTGGCTGACTATTCC GCCAATGAGAAATCTAGCCTTAGGCGTAATCAACACAT TGGAGTGGATACCGAGATTCAAGGTTAGTCCCAACCTC TTCACTGTCCCAATTAAGGAAGCAGGCGAAGACTGCCA TGCCCCAACATACCTACCTGCGGAGGTGGACGGTGATG TCAAACTCAGTTCCAACCTGGTGATTCTACCTGGTCAA GATCTCCAATATGTTTTGGCAACCTACGATACCTCCAG GGTTGAGCATGCTGTGGTTTATTACGTTTACAGCCCAA GCCGCTCATTTTCTTACTTTTATCCTTTTAGGTTGCCTAT AAAGGGGGTCCCAATCGAACTACAAGTGGAATGCTTCA CATGGGATCAAAAACTCTGGTGCCGTCACTTCTGTGTG CTTGCGGACTCAGAATCCGGTGGACTTATCACTCACTCT GGGATGGTGGGCATGGGAGTCAGCTGCACAGCTACCCG GGAAGATGGAACCAATCGCAGATAA	42
GC_H_MEASLES_B3 mRNA Sequence (assumes T100 tail) Sequence Length: 2126	G*GGGAAATAAGAGAGAAAAGAAGAGTAAGAAGAAAT ATAAGAGCCACCATGTCACCGCAACGAGACCGGATAA ATGCCTTCTACAAAGATAACCCTTATCCCAAGGGAAGT AGGATAGTTATTAACAGAGAACATCTTATGATTGACAG ACCCTATGTTCTGCTGGCTGTTCTGTTCGTCATGTTTCT GAGCTTGATCGGATTGCTGGCAATTGCAGGCATTAGAC	43

TABLE 13-continued

MeV Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
	TTCATCGGGCAGCCATCTACACCGCGGAGATCCATAAA	
	AGCCTCAGTACCAATCTGGATGTGACTAACTCCATCGA	
	GCATCAGGTCAAGGACGTGCTGACACCACTCTTTAAAA	
	TCATCGGGGATGAAGTGGGCCTGAGAACACCTCAGAG	
	ATTCACTGACCTAGTGAAATTCATCTCGGACAAGATTA	
	AATTCCTTAATCCGGATAGGGAGTACGACTTCAGAGAT	
	CTCACTTGGTGCATCAACCCGCCAGAGAGGATCAAACT	
	AGATTATGATCAATACTGTGCAGATGTGGCTGCTGAAG	
	AGCTCATGAATGCATTGGTGAACTCAACTCTACTGGAG	
	ACCAGAACAACCACTCAGTTCCTAGCTGTCTCAAAGGG	
	AAACTGCTCAGGGCCCACTACAATCAGAGGTCAATTCT	
	CAAACATGTCGCTGTCCTTGTTGGACTTGTACTTAGGTC	
	GAGGTTACAATGTGTCATCTATAGTCACTATGACATCC	
	CAGGGAATGTATGGGGGAACCTACCTAGTTGAAAAGCC	
	TAATCTGAACAGCAAAGGGTCAGAGTTGTCACAACTGA	
	GCATGTACCGAGTGTTTGAAGTAGGTGTGATCAGAAAC	
	CCGGGTTTGGGGGCTCCGGTGTTCCATATGACAAACTA	
	TTTTGAGCAACCAGTCAGTAATGGTCTCGGCAACTGTA	
	TGGTGGCTTTGGGGGAGCTCAAACTCGCAGCCCTTTGT	
	CACGGGGACGATTCTATCATAATTCCCTATCAGGGATC	
	AGGGAAAGGTGTCAGCTTCCAGCTCGTCAAGCTGGGTG	
	TCTGGAAATCCCCAACCGACATGCAATCCTGGGTCCCC	
	TTATCAACGGATGATCCAGTGGTAGACAGGCTTTACCT	
	CTCATCTCACAGAGGTGTCATCGCTGACAATCAAGCAA	
	AATGGGCTGTCCCGACAACACGAACAGATGACAAGTTG	
	CGAATGGAGACATGCTTCCAGCAGGCGTGTAAAGGTAA	
	AATCCAAGCACTCTGCGAGAATCCCGAGTGGGTACCAT	
	TGAAGGATAACAGGATTCCTTCATACGGGGTCCTGTCT	
	GTTGATCTGAGTCTGACGGTTGAGCTTAAAATCAAAAT	
	TGCTTCGGGATTCGGGCCATTGATCACACACGGCTCAG	
	GGATGGACCTATACAAATCCAACTGCAACAATGTGTAT	
	TGGCTGACTATTCCGCCAATGAGAAATCTAGCCTTAGG	
	CGTAATCAACACATTGGAGTGGATACCGAGATTCAAGG	
	TTAGTCCCAACCTCTTCACTGTCCCAATTAAGGAAGCA	
	GGCGAAGACTGCCATGCCCCAACATACCTACCTGCGGA	
	GGTGGACGGTGATGTCAAACTCAGTTCCAACCTGGTGA	
	TTCTACCTGGTCAAGATCTCCAATATGTTTTGGCAACCT	
	ACGATACCTCCAGGGTTGAGCATGCTGTGGTTTATTAC	
	GTTTACAGCCCAAGCCGCTCATTTTCTTACTTTTATCCT	
	TTTAGGTTGCCTATAAAGGGGGTCCCAATCGAACTACA	
	AGTGGAATGCTTCACATGGGATCAAAAACTCTGGTGCC	
	GTCACTTCTGTGTGCTTGCGGACTCAGAATCCGGTGGA	
	CTTATCACTCACTCTGGGATGGTGGGCATGGGAGTCAG	
	CTGCACAGCTACCCGGGAAGATGGAACCAATCGCAGAT	
	AATGATAATAGGCTGGAGCCTCGGTGGCCAAGCTTCTT	
	GCCCCTTGGGCCTCCCCCCAGCCCCTCCTCCCCTTCCTG	
	CACCCGTACCCCCGTGGTCTTTGAATAAAGTCTGAGTG	
	GGCGGCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAATC	
	TAG	
GC_H_MEASLES_D8 Sequence, NT (5' UTR, ORF, 3' UTR) Sequence Length: 2065	TCAAGCTTTTGGACCCTCGTACAGAAGCTAATACGACT CACTATAGGGAAATAAGAGAGAAAAGAAGAGTAAGAA GAAATATAAGAGCCACCATGTCACCACAACGAGACCG GATAAATGCCTTCTACAAAGACAACCCCCATCCTAAGG GAAGTAGGATAGTTATTAACAGAGAACATCTTATGATT GATAGACCTTATGTTTTGCTGGCTGTTCTATTCGTCATG TTTCTGAGCTTGATCGGGTTGCTAGCCATTGCAGGCATT AGACTTCATCGGGCAGCCATCTACACCGCAGAGATCCA TAAAAGCCTCAGCACCAATCTGGATGTAACTAACTCAA TCGAGCATCAGGTTAAGGACGTGCTGACACCACTCTTC AAGATCATCGGTGATGAAGTGGGCTTGAGGACACCTCA GAGATTCACTGACCTAGTGAAGTTCATCTCTGACAAGA TTAAATTCCTTAATCCGGACAGGGAATACGACTTCAGA GATCTCACTTGGTGTATCAACCCGCCAGAGAGAATCAA ATTGGATTATGATCAATACTGTGCAGATGTGGCTGCTG AAGAACTCATGAATGCATTGGTGAACTCAACTCTACTG GAGACCAGGGCAACCAATCAGTTCCTAGCTGTCTCAAA GGGAAACTGCTCAGGGCCCACTACAATCAGAGGCCAAT TCTCAAACATGTCGCTGTCCCTGTTGGACTTGTATTTAA GTCGAGGTTACAATGTGTCATCTATAGTCACTATGACA TCCCAGGGAATGTACGGGGGAACTTACCTAGTGGAAAA GCCTAATCTGAGCAGCAAAGGGTCAGAGTTGTCACAAC TGAGCATGCACCGAGTGTTTGAAGTAGGTGTTATCAGA	44

TABLE 13-continued

MeV Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
	AATCCGGGTTTGGGGGCTCCGGTATTCCATATGACAAA	
	CTATCTTGAGCAACCAGTCAGTAATGATTTCAGCAACT	
	GCATGGTGGCTTTGGGGGAGCTCAAGTTCGCAGCCCTC	
	TGTCACAGGGAAGATTCTATCACAATTCCCTATCAGGG	
	ATCAGGGAAAGGTGTCAGCTTCCAGCTTGTCAAGCTAG	
	GTGTCTGGAAATCCCCAACCGACATGCAATCCTGGGTC	
	CCCCTATCAACGGATGATCCAGTGATAGACAGGCTTTA	
	CCTCTCATCTCACAGAGGCGTTATCGCTGACAATCAAG	
	CAAAATGGGCTGTCCCGACAACACGGACAGATGACAA	
	GTTGCGAATGGAGACATGCTTCCAGCAGGCGTGTAAGG	
	GTAAAATCCAAGCACTTTGCGAGAATCCCGAGTGGACA	
	CCATTGAAGGATAACAGGATTCCTTCATACGGGGTCTT	
	GTCTGTTGATCTGAGTCTGACAGTTGAGCTTAAAATCA	
	AAATTGTTTCAGGATTCGGGCCATTGATCACACACGGT	
	TCAGGGATGGACCTATACAAATCCAACCACAACAATAT	
	GTATTGGCTGACTATCCCGCCAATGAAGAACCTGGCCT	
	TAGGTGTAATCAACACATTGGAGTGGATACCGAGATTC	
	AAGGTTAGTCCCAACCTCTTCACTGTTCCAATTAAGGA	
	AGCAGGCGAGGACTGCCATGCCCCAACATACCTACCTG	
	CGGAGGTGGATGGTGATGTCAAACTCAGTTCCAATCTG	
	GTGATTCTACCTGGTCAAGATCTCCAATATGTTCTGGCA	
	ACCTACGATACTTCCAGAGTTGAACATGCTGTAGTTTAT	
	TACGTTTACAGCCCAAGCCGCTCATTTTCTTACTTTTAT	
	CCTTTTAGGTTGCCTGTAAGGGGGGTCCCCATTGAATTA	
	CAAGTGGAATGCTTCACATGGGACCAAAAACTCTGGTG	
	CCGTCACTTCTGTGTGCTTGCGGACTCAGAATCTGGTGG	
	ACATATCACTCACTCTGGGATGGTGGGCATGGGAGTCA	
	GCTGCACAGCCACTCGGGAAGATGGAACCAGCCGCAG	
	ATAGTGATAATAGGCTGGAGCCTCGGTGGCCAAGCTTC	
	TTGCCCCTTGGGCCTCCCCCCAGCCCCTCCTCCCCTTCC	
	TGCACCCGTACCCCCGTGGTCTTTGAATAAAGTCTGAG	
	TGGGCGGC	
GC_H_MEASLES_D8 ORF Sequence, NT	ATGTCACCACAACGAGACCGGATAAATGCCTTCTACAA	45
	AGACAACCCCCATCCTAAGGGAAGTAGGATAGTTATTA	
	ACAGAGAACATCTTATGATTGATAGACCTTATGTTTTGC	
	TGGCTGTTCTATTCGTCATGTTTCTGAGCTTGATCGGGT	
	TGCTAGCCATTGCAGGCATTAGACTTCATCGGGCAGCC	
	ATCTACACCGCAGAGATCCATAAAAGCCTCAGCACCAA	
	TCTGGATGTAACTAACTCAATCGAGCATCAGGTTAAGG	
	ACGTGCTGACACCACTCTTCAAGATCATCGGTGATGAA	
	GTGGGCTTGAGGACACCTCAGAGATTCACTGACCTAGT	
	GAAGTTCATCTCTGACAAGATTAAATTCCTTAATCCGG	
	ACAGGGAATACGACTTCAGAGATCTCACTTGGTGTATC	
	AACCCGCCAGAGAGAATCAAATTGGATTATGATCAATA	
	CTGTGCAGATGTGGCTGCTGAAGAACTCATGAATGCAT	
	TGGTGAACTCAACTCTACTGGAGACCAGGGCAACCAAT	
	CAGTTCCTAGCTGTCTCAAAGGGAAACTGCTCAGGGCC	
	CACTACAATCAGAGGCCAATTCTCAAACATGTCGCTGT	
	CCCTGTTGGACTTGTATTTAAGTCGAGGTTACAATGTGT	
	CATCTATAGTCACTATGACATCCCAGGGAATGTACGGG	
	GGAACTTACCTAGTGGAAAAGCCTAATCTGAGCAGCAA	
	AGGGTCAGAGTTGTCACAACTGAGCATGCACCGAGTGT	
	TTGAAGTAGGTGTTATCAGAAATCCGGGTTTGGGGGCT	
	CCGGTATTCCATATGACAAACTATCTTGAGCAACCAGT	
	CAGTAATGATTTCAGCAACTGCATGGTGGCTTTGGGGG	
	AGCTCAAGTTCGCAGCCCTCTGTCACAGGGAAGATTCT	
	ATCACAATTCCCTATCAGGGATCAGGGAAAGGTGTCAG	
	CTTCCAGCTTGTCAAGCTAGGTGTCTGGAAATCCCCAA	
	CCGACATGCAATCCTGGGTCCCCCTATCAACGGATGAT	
	CCAGTGATAGACAGGCTTTACCTCTCATCTCACAGAGG	
	CGTTATCGCTGACAATCAAGCAAAATGGGCTGTCCCGA	
	CAACACGGACAGATGACAAGTTGCGAATGGAGACATG	
	CTTCCAGCAGGCGTGTAAGGGTAAAATCCAAGCACTTT	
	GCGAGAATCCCGAGTGGACACCATTGAAGGATAACAG	
	GATTCCTTCATACGGGGTCTTGTCTGTTGATCTGAGTCT	
	GACAGTTGAGCTTAAAATCAAAATTGTTTCAGGATTCG	
	GGCCATTGATCACACACGGTTCAGGGATGGACCTATAC	
	AAATCCAACCACAACAATATGTATTGGCTGACTATCCC	
	GCCAATGAAGAACCTGGCCTTAGGTGTAATCAACACAT	
	TGGAGTGGATACCGAGATTCAAGGTTAGTCCCAACCTC	
	TTCACTGTTCCAATTAAGGAAGCAGGCGAGGACTGCCA	
	TGCCCCAACATACCTACCTGCGGAGGTGGATGGTGATG	
	TCAAACTCAGTTCCAATCTGGTGATTCTACCTGGTCAAG	
	ATCTCCAATATGTTCTGGCAACCTACGATACTTCCAGA	

TABLE 13-continued

MeV Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
	GTTGAACATGCTGTAGTTTATTACGTTTACAGCCCAAGC CGCTCATTTTCTTACTTTTATCCTTTTAGGTTGCCTGTAA GGGGGGTCCCCATTGAATTACAAGTGGAATGCTTCACA TGGGACCAAAAACTCTGGTGCCGTCACTTCTGTGTGCTT GCGGACTCAGAATCTGGTGGACATATCACTCACTCTGG GATGGTGGGCATGGGAGTCAGCTGCACAGCCACTCGGG AAGATGGAACCAGCCGCAGATAG	
GC_H_MEASLES_D8 mRNA Sequence (assumes T100 tail) Sequence Length: 2126	G*GGGAAATAAGAGAGAAAAGAAGAGTAAGAAGAAAT ATAAGAGCCACCATGTCACCACAACGAGACCGGATAA ATGCCTTCTACAAAGACAACCCCCATCCTAAGGGAAGT AGGATAGTTATTAACAGAGAACATCTTATGATTGATAG ACCTTATGTTTTGCTGGCTGTTCTATTCGTCATGTTTCTG AGCTTGATCGGGTTGCTAGCCATTGCAGGCATTAGACT TCATCGGGCAGCCATCTACACCGCAGAGATCCATAAAA GCCTCAGCACCAATCTGGATGTAACTAACTCAATCGAG CATCAGGTTAAGGACGTGCTGACACCACTCTTCAAGAT CATCGGTGATGAAGTGGGCTTGAGGACACCTCAGAGAT TCACTGACCTAGTGAAGTTCATCTCTGACAAGATTAAA TTCCTTAATCCGGACAGGGAATACGACTTCAGAGATCT CACTTGGTGTATCAACCCGCCAGAGAGAATCAAATTGG ATTATGATCAATACTGTGCAGATGTGGCTGCTGAAGAA CTCATGAATGCATTGGTGAACTCAACTCTACTGGAGAC CAGGGCAACCAATCAGTTCCTAGCTGTCTCAAAGGGAA ACTGCTCAGGGCCCACTACAATCAGAGGCCAATTCTCA AACATGTCGCTGTCCCTGTTGGACTTGTATTTAAGTCGA GGTTACAATGTGTCATCTATAGTCACTATGACATCCCA GGGAATGTACGGGGGAACTTACCTAGTGGAAAAGCCT AATCTGAGCAGCAAAGGGTCAGAGTTGTCACAACTGAG CATGCACCGAGTGTTTGAAGTAGGTGTTATCAGAAATC CGGGTTTGGGGGCTCCGGTATTCCATATGACAAACTAT CTTGAGCAACCAGTCAGTAATGATTTCAGCAACTGCAT GGTGGCTTTGGGGGAGCTCAAGTTCGCAGCCCTCTGTC ACAGGGAAGATTCTATCACAATTCCCTATCAGGGATCA GGGAAAGGTGTCAGCTTCCAGCTTGTCAAGCTAGGTGT CTGGAAATCCCCAACCGACATGCAATCCTGGGTCCCCC TATCAACGGATGATCCAGTGATAGACAGGCTTTACCTC TCATCTCACAGAGGCGTTATCGCTGACAATCAAGCAAA ATGGGCTGTCCCGACAACACGGACAGATGACAAGTTGC GAATGGAGACATGCTTCCAGCAGGCGTGTAAGGGTAA AATCCAAGCACTTTGCGAGAATCCCGAGTGGACACCAT TGAAGGATAACAGGATTCCTTCATACGGGGTCTTGTCT GTTGATCTGAGTCTGACAGTTGAGCTTAAAATCAAAAT TGTTTCAGGATTCGGGCCATTGATCACACACGGTTCAG GGATGGACCTATACAAATCCAACCACAACAATATGTAT TGGCTGACTATCCCGCCAATGAAGAACCTGGCCTTAGG TGTAATCAACACATTGGAGTGGATACCGAGATTCAAGG TTAGTCCCAACCTCTTCACTGTTCCAATTAAGGAAGCA GGCGAGGACTGCCATGCCCCAACATACCTACCTGCGGA GGTGGATGGTGATGTCAAACTCAGTTCCAATCTGGTGA TTCTACCTGGTCAAGATCTCCAATATGTTCTGGCAACCT ACGATACTTCCAGAGTTGAACATGCTGTAGTTTATTAC GTTTACAGCCCAAGCCGCTCATTTTCTTACTTTTATCCT TTTAGGTTGCCTGTAAGGGGGGTCCCCATTGAATTACA AGTGGAATGCTTCACATGGGACCAAAAACTCTGGTGCC GTCACTTCTGTGTGCTTGCGGACTCAGAATCTGGTGGA CATATCACTCACTCTGGGATGGTGGGCATGGGAGTCAG CTGCACAGCCACTCGGGAAGATGGAACCAGCCGCAGA TAGTGATAATAGGCTGGAGCCTCGGTGGCCAAGCTTCT TGCCCCTTGGGCCTCCCCCCAGCCCCTCCTCCCCTTCCT GCACCCGTACCCCCGTGGTCTTTGAATAAAGTCTGAGT GGGCGGCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAT CTAG	46
MeV mRNA Sequences		
GC_F_MEASLES_B3.1 Sequence, NT (5' UTR, ORF, 3' UTR) Sequence Length: 1864	UCAAGCUUUUGGACCCUCGUACAGAAGCUAAUACGAC UCACUAUAGGGAAAUAAGAGAGAAAAGAAGAGUAAG AAGAAAUAUAAGAGCCACCAUGGGUCUCAAGGUGAA CGUCUCUGCCGUAUUCAUGGCAGUACUGUUAACUCUC CAAACACCCGCCGGUCAAAUUCAUUGGGGCAAUCUCU CUAAGAUAGGGGUAGUAGGAAUAGGAAGUGCAAGCU ACAAAGUUAUGACUCGUUCCAGCCAUCAAUCAUUAGU	69

TABLE 13-continued

MeV Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
	CAUAAAAUUAAUGCCCAAUAUAACUCUCCUCAAUAAC	
	UGCACGAGGGUAGAGAUUGCAGAAUACAGGAGACUA	
	CUAAGAACAGUUUUGGAACCAAUUAGGGAUGCACUU	
	AAUGCAAUGACCCAGAACAUAAGGCCGGUUCAGAGCG	
	UAGCUUCAAGUAGGAGACACAAGAGAUUUGCGGGAG	
	UAGUCCUGGCAGGUGCGGCCCUAGGUGUUGCCACAGC	
	UGCUCAGAUAACAGCCGGCAUUGCACUUCACCGGUCC	
	AUGCUGAACUCUCAGGCCAUCGACAAUCUGAGAGCGA	
	GCCUGGAAACUACUAAUCAGGCAAUUGAGGCAAUCAG	
	ACAAGCAGGGCAGGAGAUGAUAUUGGCUGUUCAGGG	
	UGUCCAAGACUACAUCAAUAAUGAGCUGAUACCGUCU	
	AUGAACCAGCUAUCUUGUGAUCUAAUCGGUCAGAAGC	
	UCGGGCUCAAAUUGCUUAGAUACUAUACAGAAAUCCU	
	GUCAUUAUUUGGCCCCAGCCUACGGGACCCCAUAUCU	
	GCGGAGAUAUCUAUCCAGGCUUUGAGUUAUGCACUU	
	GGAGGAGAUAUCAAUAAGGUGUUAGAAAAGCUCGGA	
	UACAGUGGAGGCGAUUUACUAGGCAUCUUAGAGAGC	
	AGAGGAAUAAAGGCUCGGAUAACUCACGUCGACACAG	
	AGUCCUACUUCAUAGUCCUCAGUAUAGCCUAUCCGAC	
	GCUGUCCGAGAUUAAGGGGGUGAUUGUCCACCGGCUA	
	GAGGGGGUCUCGUACAACAUAGGCUCUCAAGAGUGG	
	UAUACCACUGUGCCCAAGUAUGUUGCAACCCAAGGGU	
	ACCUUAUCUCGAAUUUUGAUGAGUCAUCAUGUACUU	
	UCAUGCCAGAGGGGACUGUGUGCAGCCAAAAUGCCUU	
	GUACCCGAUGAGUCCUCUGCUCCAAGAAUGCCUCCGG	
	GGGUCCACCAAGUCCUGUGCUCGUACACUCGUAUCCG	
	GGUCUUUUGGGAACCGGUUCAUUUUAUCACAAGGGA	
	ACCUAAUAGCCAAUUGUGCAUCAAUUCUUUGUAAGU	
	GUUACACAACAGGUACGAUUAUUAAUCAAGACCCUGA	
	CAAGAUCCUAACAUACAUUGCUGCCGAUCGCUGCCCG	
	GUAGUCGAGGUGAACGGCGUGACCAUCCAAGUCGGGA	
	GCAGGAGGUAUCCAGACGCUGUGUACUUGCACAGAAU	
	UGACCUCGGUCCUCCCAUAUCAUUGGAGAGGUUGGAC	
	GUAGGGACAAAUCUGGGGAAUGCAAUUGCCAAAUUG	
	GAGGAUGCCAAGGAAUUGUUGGAAUCAUCGGACCAG	
	AUAUUGAGAAGUAUGAAAGGUUUAUCGAGCACUAGC	
	AUAGUCUACAUCCUGAUUGCAGUGUGUCUUGGAGGG	
	UUGAUAGGGAUCCCCACUUUAAUAUGUUGCUGCAGG	
	GGGCGUUGUAACAAAAAGGGAGAACAAGUUGGUAUG	
	UCAAGACCAGGCCUAAAGCCUGACCUUACAGGAACAU	
	CAAAAUCCUAUGUAAGAUCGCUUUGAUGAUAAUAGG	
	CUGGAGCCUCGGUGGCCAAGCUUCUUGCCCCUUGGGC	
	CUCCCCCCAGCCCCUCCUCCCCUUCCUGCACCCGUACC	
	CCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGGC	
GC_F_MEASLES_B3.1 ORF Sequence, NT	AUGGGUCUCAAGGUGAACGUCUCUGCCGUAUUCAUGG	70
	CAGUACUGUUAACUCUCCAAACACCCGCCGGUCAAAU	
	UCAUUGGGGCAAUCUCUCUAAGAUAGGGGUAGUAGG	
	AAUAGGAAGUGCAAGCUACAAAGUUAUGACUCGUUC	
	CAGCCAUCAAUCAUUAGUCAUAAAAUUAAUGCCCAAU	
	AUAACUCUCCUCAAUAACUGCACGAGGGUAGAGAUUG	
	CAGAAUACAGGAGACUACUAAGAACAGUUUUGGAAC	
	CAAUUAGGGAUGCACUUAAUGCAAUGACCCAGAACAU	
	AAGGCCGGUUCAGAGCGUAGCUUCAAGUAGGAGACAC	
	AAGAGAUUUGCGGGAGUAGUCCUGGCAGGUGCGGCCC	
	UAGGUGUUGCCACAGCUGCUCAGAUAACAGCCGGCAU	
	UGCACUUCACCGGUCCAUGCUGAACUCUCAGGCCAUC	
	GACAAUCUGAGAGCGAGCCUGGAAACUACUAAUCAGG	
	CAAUUGAGGCAAUCAGACAAGCAGGGCAGGAGAUGA	
	UAUUGGCUGUUCAGGGUGUCCAAGACUACAUCAAUA	
	AUGAGCUGAUACCGUCUAUGAACCAGCUAUCUUGUGA	
	UCUAAUCGGUCAGAAGCUCGGGCUCAAAUUGCUUAGA	
	UACUAUACAGAAAUCCUGUCAUUAUUUGGCCCCAGCC	
	UACGGGACCCCAUAUCUGCGGAGAUAUCUAUCCAGGC	
	UUUGAGUUAUGCACUUGGAGGAGAUAUCAAUAAGGU	
	GUUAGAAAAGCUCGGAUACAGUGGAGGCGAUUUACU	
	AGGCAUCUUAGAGAGCAGAGGAAUAAAGGCUCGGAU	
	AACUCACGUCGACACAGAGUCCUACUUCAUAGUCCUC	
	AGUAUAGCCUAUCCGACGCUGUCCGAGAUUAAGGGGG	
	UGAUUGUCCACCGGCUAGAGGGGGUCUCGUACAACAU	
	AGGCUCUCAAGAGUGGUAUACCACUGUGCCCAAGUAU	
	GUUGCAACCCAAGGGUACCUUAUCUCGAAUUUUGAUG	
	AGUCAUCAUGUACUUUCAUGCCAGAGGGGACUGUGU	
	GCAGCCAAAAUGCCUUGUACCCGAUGAGUCCUCUGCU	
	CCAAGAAUGCCUCCGGGGGUCCACCAAGUCCUGUGCU	

TABLE 13-continued

MeV Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
	CGUACACUCGUAUCCGGGUCUUUUGGGAACCGGUUCA UUUUAUCACAAGGGAACCUAAUAGCCAAUUGUGCAUC AAUUCUUUGUAAGUGUUACACAACAGGUACGAUUAU UAAUCAAGACCCUGACAAGAUCCUAACAUACAUUGCU GCCGAUCGCUGCCCGGUAGUCGAGGUGAACGGCGUGA CCAUCCAAGUCGGGAGCAGGAGGUAUCCAGACGCUGU GUACUUGCACAGAAUUGACCUCGGUCCUCCCAUAUCA UUGGAGAGGUUGGACGUAGGGACAAAUCUGGGGAAU GCAAUUGCCAAAUUGGAGGAUGCCAAGGAAUUGUUG GAAUCAUCGGACCAGAUAUUGAGAAGUAUGAAAGGU UUAUCGAGCACUAGCAUAGUCUACAUCCUGAUUGCAG UGUGUCUUGGAGGGUUGAUAGGGAUCCCCACUUUAA UAUGUUGCUGCAGGGGGCGUUGUAACAAAAAGGGAG AACAAGUUGGUAUGUCAAGACCAGGCCUAAAGCCUGA CCUUACAGGAACAUCAAAAUCCUAUGUAAGAUCGCUU UGA	
GC_F_MEASLES_B3.1 mRNA Sequence (assumes T100 tail) mRNA Sequence Length: 1925	G*GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAA UAUAAGAGCCACCAUGGGUCUCAAGGUGAACGUCUCU GCCGUAUUCAUGGCAGUACUGUUAACUCUCCAAACAC CCGCCGGUCAAAUUCAUUGGGGCAAUCUCUCUAAGAU AGGGGUAGUAGGAAUAGGAAGUGCAAGCUACAAAGU UAUGACUCGUUCCAGCCAUCAAUCAUUAGUCAUAAAA UUAAUGCCCAAUAUAACUCUCCUCAAUAACUGCACGA GGGUAGAGAUUGCAGAAUACAGGAGACUACUAAGAA CAGUUUUGGAACCAAUUAGGGAUGCACUUAAUGCAA UGACCCAGAACAUAAGGCCGGUUCAGAGCGUAGCUUC AAGUAGGAGACACAAGAGAUUUGCGGGAGUAGUCCU GGCAGGUGCGGCCCUAGGUGUUGCCACAGCUGCUCAG AUAACAGCCGGCAUUGCACUUCACCGGUCCAUGCUGA ACUCUCAGGCCAUCGACAAUCUGAGAGCGAGCCUGGA AACUACUAAUCAGGCAAUUGAGGCAAUCAGACAAGCA GGGCAGGAGAUGAUAUUGGCUGUUCAGGGUGUCCAA GACUACAUCAAUAAUGAGCUGAUACCGUCUAUGAACC AGCUAUCUUGUGAUCUAAUCGGUCAGAAGCUCGGGCU CAAAUUGCUUAGAUACUAUACAGAAAUCCUGUCAUU AUUUGGCCCCAGCCUACGGGACCCCAUAUCUGCGGAG AUAUCUAUCCAGGCUUUGAGUUAUGCACUUGGAGGA GAUAUCAAUAAGGUGUUAGAAAAGCUCGGAUACAGU GGAGGCGAUUUACUAGGCAUCUUAGAGAGCAGAGGA AUAAAGGCUCGGAUAACUCACGUCGACACAGAGUCCU ACUUCAUAGUCCUCAGUAUAGCCUAUCCGACGCUGUC CGAGAUUAAGGGGGUGAUUGUCCACCGGCUAGAGGG GGUCUCGUACAACAUAGGCUCUCAAGAGUGGUAUACC ACUGUGCCCAAGUAUGUUGCAACCCAAGGGUACCUUA UCUCGAAUUUUGAUGAGUCAUCAUGUACUUUCAUGCC AGAGGGGACUGUGUGCAGCCAAAAUGCCUUGUACCCG AUGAGUCCUCUGCUCCAAGAAUGCCUCCGGGGGUCCA CCAAGUCCUGUGCUCGUACACUCGUAUCCGGGUCUUU UGGGAACCGGUUCAUUUUAUCACAAGGGAACCUAAU AGCCAAUUGUGCAUCAAUUCUUUGUAAGUGUUACAC AACAGGUACGAUUAUUAAUCAAGACCCUGACAAGAUC CUAACAUACAUUGCUGCCGAUCGCUGCCCGGUAGUCG AGGUGAACGGCGUGACCAUCCAAGUCGGGAGCAGGAG GUAUCCAGACGCUGUGUACUUGCACAGAAUUGACCUC GGUCCUCCCAUAUCAUUGGAGAGGUUGGACGUAGGG ACAAAUCUGGGGAAUGCAAUUGCCAAAUUGGAGGAU GCCAAGGAAUUGUUGGAAUCAUCGGACCAGAUAUUG AGAAGUAUGAAAGGUUUAUCGAGCACUAGCAUAGUC UACAUCCUGAUUGCAGUGUGUCUUGGAGGGUUGAUA GGGAUCCCCACUUUAAUAUGUUGCUGCAGGGGGCGUU GUAACAAAAAGGGAGAACAAGUUGGUAUGUCAAGAC CAGGCCUAAAGCCUGACCUUACAGGAACAUCAAAAUC CUAUGUAAGAUCGCUUUGAUGAUAAUAGGCUGGAGC CUCGGUGGCCAAGCUUCUUGCCCCUUGGGCCUCCCCC CAGCCCCUCCUCCCCUUCCUGCACCCGUACCCCCGUGG UCUUUGAAUAAAGUCUGAGUGGGCGGCAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAUCUAG	71
GC_F_MEASLES_D8 Sequence, NT (5' UTR, ORF, 3' UTR)	UCAAGCUUUUGGACCCUCGUACAGAAGCUAAUACGAC UCACUAUAGGGAAAUAAGAGAGAAAAGAAGAGUAAG AAGAAAUAUAAGAGCCACCAUGGGUCUCAAGGUGAA CGUCUCUGUCAUAUUCAUGGCAGUACUGUUAACUCUU	72

TABLE 13-continued

MeV Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
Sequence Length: 1864	CAAACACCCACCGGUCAAAUCCAUUGGGGCAAUCUCU CUAAGAUAGGGGUGGUAGGGGUAGGAAGUGCAAGCU ACAAAGUUAUGACUCGUUCCAGCCAUCAAUCAUUAGU CAUAAAGUUAAUGCCCAAUAUAACUCUCCUCAACAAU UGCACGAGGGUAGGGAUUGCAGAAUACAGGAGACUA CUGAGAACAGUUCUGGAACCAAUUAGAGAUGCACUU AAUGCAAUGACCCAGAAUAUAAGACCGGUUCAGAGU GUAGCUUCAAGUAGGAGACACAAGAGAUUUGCGGGA GUUGUCCUGGCAGGUGCGGCCCUAGGCGUUGCCACAG CUGCUCAAAUAACAGCCGGUAUUGCACUUCACCAGUC CAUGCUGAACUCUCAAGCCAUCGACAAUCUGAGAGCG AGCCUAGAAACUACUAAUCAGGCAAUUGAGGCAAUCA GACAAGCAGGGCAGGAGAUGAUAUUGGCUGUUCAGG GUGUCCAAGACUACAUCAAUAAUGAGCUGAUACCGUC UAUGAAUCAACUAUCUUGUGAUUUAAUCGGCCAGAA GCUAGGGCUCAAAUUGCUCAGAUACUAUACAGAAAUC CUGUCAUUAUUUGGCCCCAGCUUACGGGACCCCAUAU CUGCGGAGAUAUCUAUCCAGGCUUUGAGCUAUGCGCU UGGAGGAGAUAUCAAUAAGGUGUUGGAAAAGCUCGG AUACAGUGGAGGUGAUCUACUGGGCAUCUUAGAGAG CAGAGGAAUAAAGGCCCGGAUAACUCACGUCGACACA GAGUCCUACUUCAUUGUACUCAGUAUAGCCUAUCCGA CGCUAUCCGAGAUUAAGGGGGUGAUUGUCCACCGGCU AGAGGGGGUCUCGUACAACAUAGGCUCUCAAGAGUG GUAUACCACUGUGCCCAAGUAUGUUGCAACCCAAGGG UACCUUAUCUCGAAUUUUGAUGAGUCAUCAUGCACUU UCAUGCCAGAGGGGACUGUGUGCAGCCAGAAUGCCUU GUACCCGAUGAGUCCUCUGCUCCAAGAAUGCCUCCGG GGGUCCACUAAGUCCUGUGCUCGUACACUCGUAUCCG GGUCUUUCGGGAACCGGUUCAUUUUAUCACAGGGGA ACCUAAUAGCCAAUUGUGCAUCAAUCCUUUGCAAGUG UUACACAACAGGAACAAUCAUUAAUCAAGACCCUGAC AAGAUCCUAACAUACAUUGCUGCCGAUCACUGCCCGG UGGUCGAGGUGAAUGGCGUGACCAUCCAAGUCGGGA GCAGGAGGUAUCCGGACGCUGUGUACUUGCACAGGAU UGACCUCGGUCCUCCCAUAUCUUUGGAGAGGUUGGAC GUAGGGACAAAUCUGGGGAAUGCAAUUGCUAAGUUG GAGGAUGCCAAGGAAUUGUUGGAGUCAUCGGACCAG AUAUUGAGGAGUAUGAAAGGUUUAUCGAGCACUAGU AUAGUUUACAUCCUGAUUGCAGUGUGUCUUGGAGGA UUGAUAGGGAUCCCCGCUUUAAUAUGUUGCUGCAGG GGGCGUUGUAACAAGAAGGGAGAACAAGUUGGUAUG UCAAGACCAGGCCUAAAGCCUGAUCUUACAGGAACAU CAAAAUCCUAUGUAAGGUCACUCUGAUGAUAAUAGG CUGGAGCCUCGGUGGCCAAGCUUCUUGCCCCUUGGGC CUCCCCCCAGCCCCUCCUCCCCUUCCUGCACCCGUACC CCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGGC	
GC_F_MEASLES_D8 ORF Sequence, NT	AUGGGUCUCAAGGUGAACGUCUCUGUCAUAUUCAUG GCAGUACUGUUAACUCUUCAAACACCCACCGGUCAAA UCCAUUGGGGCAAUCUCUCUAAGAUAGGGGUGGUAG GGGUAGGAAGUGCAAGCUACAAAGUUAUGACUCGUU CCAGCCAUCAAUCAUUAGUCAUAAAGUUAAUGCCCAA UAUAACUCUCCUCAACAAUUGCACGAGGGUAGGGAUU GCAGAAUACAGGAGACUACUGAGAACAGUUCUGGAA CCAAUUAGAGAUGCACUUAAUGCAAUGACCCAGAAUA UAAGACCGGUUCAGAGUGUAGCUUCAAGUAGGAGAC ACAAGAGAUUUGCGGGAGUUGUCCUGGCAGGUGCGG CCCUAGGCGUUGCCACAGCUGCUCAAAUAACAGCCGG UAUUGCACUUCACCAGUCCAUGCUGAACUCUCAAGCC AUCGACAAUCUGAGAGCGAGCCUAGAAACUACUAAUC AGGCAAUUGAGGCAAUCAGACAAGCAGGGCAGGAGA UGAUAUUGGCUGUUCAGGGUGUCCAAGACUACAUCA AUAAUGAGCUGAUACCGUCUAUGAAUCAACUAUCUU GUGAUUUAAUCGGCCAGAAGCUAGGGCUCAAAUUGC UCAGAUACUAUACAGAAAUCCUGUCAUUAUUUGGCCC CAGCUUACGGGACCCCAUAUCUGCGGAGAUAUCUAUC CAGGCUUUGAGCUAUGCGCUUGGAGGAGAUAUCAAU AAGGUGUUGGAAAAGCUCGGAUACAGUGGAGGUGAU CUACUGGGCAUCUUAGAGAGCAGAGGAAUAAAGGCCC GGAUAACUCACGUCGACACAGAGUCCUACUUCAUUGU ACUCAGUAUAGCCUAUCCGACGCUAUCCGAGAUUAAG GGGGUGAUUGUCCACCGGCUAGAGGGGGUCUCGUACA ACAUAGGCUCUCAAGAGUGGUAUACCACUGUGCCCAA GUAUGUUGCAACCCAAGGGUACCUUAUCUCGAAUUUU	73

TABLE 13-continued

MeV Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
	GAUGAGUCAUCAUGCACUUUCAUGCCAGAGGGGACUG UGUGCAGCCAGAAUGCCUUGUACCCGAUGAGUCCUCU GCUCCAAGAAUGCCUCCGGGGGUCCACUAAGUCCUGU GCUCGUACACUCGUAUCCGGGUCUUUCGGGAACCGGU UCAUUUUAUCACAGGGGAACCUAAUAGCCAAUUGUGC AUCAAUCCUUUGCAAGUGUUACACAACAGGAACAAUC AUUAAUCAAGACCCUGACAAGAUCCUAACAUACAUUG CUGCCGAUCACUGCCCGGUGGUCGAGGUGAAUGGCGU GACCAUCCAAGUCGGGAGCAGGAGGUAUCCGGACGCU GUGUACUUGCACAGGAUUGACCUCGGUCCUCCCAUAU CUUUGGAGAGGUUGGACGUAGGGACAAAUCUGGGGA AUGCAAUUGCUAAGUUGGAGGAUGCCAAGGAAUUGU UGGAGUCAUCGGACCAGAUAUUGAGGAGUAUGAAAG GUUUAUCGAGCACUAGUAUAGUUUACAUCCUGAUUG CAGUGUGUCUUGGAGGAUUGAUAGGGAUCCCCGCUU UAAUAUGUUGCUGCAGGGGGCGUUGUAACAAGAAGG GAGAACAAGUUGGUAUGUCAAGACCAGGCCUAAAGCC UGAUCUUACAGGAACAUCAAAAUCCUAUGUAAGGUC ACUCUGA	
GC_F_MEASLES_D8 mRNA Sequence (assumes T100 tail) Sequence Length: 1925	G*GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAA UAUAAGAGCCACCAUGGGUCUCAAGGUGAACGUCUCU GUCAUAUUCAUGGCAGUACUGUUAACUCUUCAAACAC CCACCGGUCAAAUCCAUUGGGGCAAUCUCUCUAAGAU AGGGGUGGUAGGGGUAGGAAGUGCAAGCUACAAAGU UAUGACUCGUUCCAGCCAUCAAUCAUUAGUCAUAAAG UUAAUGCCCAAUAUAACUCUCCUCAACAAUUGCACGA GGGUAGGGAUUGCAGAAUACAGGAGACUACUGAGAA CAGUUCUGGAACCAAUUAGAGAUGCACUUAAUGCAA UGACCCAGAAUAUAAGACCGGUUCAGAGUGUAGCUUC AAGUAGGAGACACAAGAGAUUUGCGGGAGUUGUCCU GGCAGGUGCGGCCCUAGGCGUUGCCACAGCUGCUCAA AUAACAGCCGGUAUUGCACUUCACCAGUCCAUGCUGA ACUCUCAAGCCAUCGACAAUCUGAGAGCGAGCCUAGA AACUACUAAUCAGGCAAUUGAGGCAAUCAGACAAGCA GGGCAGGAGAUGAUAUUGGCUGUUCAGGGUGUCCAA GACUACAUCAAUAAUGAGCUGAUACCGUCUAUGAAUC AACUAUCUUGUGAUUUAAUCGGCCAGAAGCUAGGGC UCAAAUUGCUCAGAUACUAUACAGAAAUCCUGUCAUU AUUUGGCCCCAGCUUACGGGACCCCAUAUCUGCGGAG AUAUCUAUCCAGGCUUUGAGCUAUGCGCUUGGAGGA GAUAUCAAUAAGGUGUUGGAAAAGCUCGGAUACAGU GGAGGUGAUCUACUGGGCAUCUUAGAGAGCAGAGGA AUAAAGGCCCGGAUAACUCACGUCGACACAGAGUCCU ACUUCAUUGUACUCAGUAUAGCCUAUCCGACGCUAUC CGAGAUUAAGGGGGUGAUUGUCCACCGGCUAGAGGG GGUCUCGUACAACAUAGGCUCUCAAGAGUGGUAUACC ACUGUGCCCAAGUAUGUUGCAACCCAAGGGUACCUUA UCUCGAAUUUUGAUGAGUCAUCAUGCACUUUCAUGCC AGAGGGGACUGUGUGCAGCCAGAAUGCCUUGUACCCG AUGAGUCCUCUGCUCCAAGAAUGCCUCCGGGGGUCCA CUAAGUCCUGUGCUCGUACACUCGUAUCCGGGUCUUU CGGGAACCGGUUCAUUUUAUCACAGGGGAACCUAAUA GCCAAUUGUGCAUCAAUCCUUUGCAAGUGUUACACAA CAGGAACAAUCAUUAAUCAAGACCCUGACAAGAUCCU AACAUACAUUGCUGCCGAUCACUGCCCGGUGGUCGAG GUGAAUGGCGUGACCAUCCAAGUCGGGAGCAGGAGG UAUCCGGACGCUGUGUACUUGCACAGGAUUGACCUCG GUCCUCCCAUAUCUUUGGAGAGGUUGGACGUAGGGAC AAAUCUGGGGAAUGCAAUUGCUAAGUUGGAGGAUGC CAAGGAAUUGUUGGAGUCAUCGGACCAGAUAUUGAG GAGUAUGAAAGGUUUAUCGAGCACUAGUAUAGUUUA CAUCCUGAUUGCAGUGUGUCUUGGAGGAUUGAUAGG GAUCCCCGCUUUAAUAUGUUGCUGCAGGGGGCGUUGU AACAAGAAGGGAGAACAAGUUGGUAUGUCAAGACCA GGCCUAAAGCCUGAUCUUACAGGAACAUCAAAAUCCU AUGUAAGGUCACUCUGAUGAUAAUAGGCUGGAGCCU CGGUGGCCAAGCUUCUUGCCCCUUGGGCCUCCCCCCA GCCCCUCCUCCCCUUCCUGCACCCGUACCCCCGUGGUC UUUGAAUAAAGUCUGAGUGGGCGGCAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAUCUAG	74

TABLE 13-continued

MeV Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
GC_H_MEASLES_B3 Sequence, NT (5' UTR, ORF, 3' UTR) Sequence Length: 2065	UCAAGCUUUUGGACCCUCGUACAGAAGCUAAUACGAC UCACUAUAGGGAAAUAAGAGAGAAAAGAAGAGUAAG AAGAAAUAUAAGAGCCACCAUGUCACCGCAACGAGAC CGGAUAAAUGCCUUCUACAAAGAUAACCCUUAUCCCA AGGGAAGUAGGAUAGUUAUUAACAGAGAACAUCUUA UGAUUGACAGACCCUAUGUUCUGCUGGCUGUUCUGUU CGUCAUGUUUCUGAGCUUGAUCGGAUUGCUGGCAAU UGCAGGCAUUAGACUUCAUCGGGCAGCCAUCUACACC GCGGAGAUCCAUAAAAGCCUCAGUACCAAUCUGGAUG UGACUAACUCCAUCGAGCAUCAGGUCAAGGACGUGCU GACACCACUCUUUAAAAUCAUCGGGGAUGAAGUGGGC CUGAGAACACCUCAGAGAUUCACUGACCUAGUGAAAU UCAUCUCGGACAAGAUUAAAUUCCUUAAUCCGGAUAG GGAGUACGACUUCAGAGAUCUCACUUGGUGCAUCAAC CCGCCAGAGAGGAUCAAACUAGAUUAUGAUCAAUACU GUGCAGAUGUGGCUGCUGAAGAGCUCAUGAAUGCAU UGGUGAACUCAACUCUACUGGAGACCAGAACAACCAC UCAGUUCCUAGCUGUCUCAAAGGGAAACUGCUCAGGG CCCACUACAAUCAGAGGUCAAUUCUCAAACAUGUCGC UGUCCUUGUUGGACUUGUACUUAGGUCGAGGUUACA AUGUGUCAUCUAUAGUCACUAUGACAUCCCAGGGAAU GUAUGGGGGAACCUACCUAGUUGAAAAGCCUAAUCU GAACAGCAAAGGGUCAGAGUUGUCACAACUGAGCAU GUACCGAGUGUUUGAAGUAGGUGUGAUCAGAAACCC GGGUUUGGGGGCUCCGGUGUUCCAUAUGACAAACUA UUUUGAGCAACCAGUCAGUAAUGGUCUCGGCAACUGU AUGGUGGCUUUGGGGGAGCUCAAACUCGCAGCCCUUU GUCACGGGGACGAUUCUAUCAUAAUUCCCUAUCAGGG AUCAGGGAAAGGUGUCAGCUUCCAGCUCGUCAAGCUG GGUGUCUGGAAAUCCCCAACCGACAUGCAAUCCUGGG UCCCCUUAUCAACGGAUGAUCCAGUGGUAGACAGGCU UUACCUCUCAUCUCACAGAGGUGUCAUCGCUGACAAU CAAGCAAAAUGGGCUGUCCCGACAACACGAACAGAUG ACAAGUUGCGAAUGGAGACAUGCUUCCAGCAGGCGUG UAAAGGUAAAAUCCAAGCACUCUGCGAGAAUCCCGAG UGGGUACCAUUGAAGGAUAACAGGAUUCCUUCAUAC GGGGUCCUGUCUGUUGAUCUGAGUCUGACGGUUGAG CUUAAAAUCAAAAUUGCUUCGGGAUUCGGGCCAUUG AUCACACACGGCUCAGGGAUGGACCUAUACAAAUCCA ACUGCAACAAUGUGUAUUGGCUGACUAUUCCGCCAAU GAGAAAUCUAGCCUUAGGCGUAAUCAACACAUUGGA GUGGAUACCGAGAUUCAAGGUUAGUCCCAACCUCUUC ACUGUCCCAAUUAAGGAAGCAGGCGAAGACUGCCAUG CCCCAACAUACCUACCUGCGGAGGUGGACGGUGAUGU CAAACUCAGUUCCAACCUGGUGAUUCUACCUGGUCAA GAUCUCCAAUAUGUUUUGGCAACCUACGAUACCUCCA GGGUUGAGCAUGCUGUGGUUUAUUACGUUUACAGCC CAAGCCGCUCAUUUUCUUACUUUUAUCCUUUUAGGUU GCCUAUAAAGGGGGUCCCAAUCGAACUACAAGUGGAA UGCUUCACAUGGGAUCAAAAACUCUGGUGCCGUCACU UCUGUGUGCUUGCGGACUCAGAAUCCGGUGGACUUAU CACUCACUCUGGGAUGGUGGGCAUGGGAGUCAGCUGC ACAGCUACCCGGGAAGAUGGAACCAAUCGCAGAUAAU GAUAAUAGGCUGGAGCCUCGGUGGCCAAGCUUCUUGC CCCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGC ACCCGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUG GGCGGC	75
GC_H_MEASLES_B3 ORF Sequence, NT	AUGUCACCGCAACGAGACCGGAUAAAUGCCUUCUACA AAGAUAACCCUUAUCCCAAGGGAAGUAGGAUAGUUA UUAACAGAGAACAUCUUAUGAUUGACAGACCCUAUG UUCUGCUGGCUGUUCUGUUCGUCAUGUUUCUGAGCUU GAUCGGAUUGCUGGCAAUUGCAGGCAUUAGACUUCA UCGGGCAGCCAUCUACACCGCGGAGAUCCAUAAAAGC CUCAGUACCAAUCUGGAUGUGACUAACUCCAUCGAGC AUCAGGUCAAGGACGUGCUGACACCACUCUUUAAAAU CAUCGGGGAUGAAGUGGGCCUGAGAACACCUCAGAGA UUCACUGACCUAGUGAAAUUCAUCUCGGACAAGAUUA AAUUCCUUAAUCCGGAUAGGGAGUACGACUUCAGAG AUCUCACUUGGUGCAUCAACCCGCCAGAGAGGAUCAA ACUAGAUUAUGAUCAAUACUGUGCAGAUGUGGCUGC UGAAGAGCUCAUGAAUGCAUUGGUGAACUCAACUCU ACUGGAGACCAGAACAACCACUCAGUUCCUAGCUGUC UCAAAGGGAAACUGCUCAGGGCCCACUACAAUCAGAG	76

TABLE 13-continued

MeV Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
	GUCAAUUCUCAAACAUGUCGCUGUCCUUGUUGGACUU	
	GUACUUAGGUCGAGGUUACAAUGUGUCAUCUAUAGU	
	CACUAUGACAUCCCAGGGAAUGUAUGGGGGAACCUAC	
	CUAGUUGAAAAGCCUAAUCUGAACAGCAAAGGGUCA	
	GAGUUGUCACAACUGAGCAUGUACCGAGUGUUUGAA	
	GUAGGUGUGAUCAGAAACCCGGGUUUGGGGGCUCCG	
	GUGUUCCAUAUGACAAACUAUUUUGAGCAACCAGUCA	
	GUAAUGGUCUCGGCAACUGUAUGGUGGCUUUGGGGG	
	AGCUCAAACUCGCAGCCCUUUGUCACGGGGACGAUUC	
	UAUCAUAAUUCCCUAUCAGGGAUCAGGGAAAGGUGU	
	CAGCUUCCAGCUCGUCAAGCUGGGUGUCUGGAAAUCC	
	CCAACCGACAUGCAAUCCUGGGUCCCCUUAUCAACGG	
	AUGAUCCAGUGGUAGACAGGCUUUACCUCUCAUCUCA	
	CAGAGGUGUCAUCGCUGACAAUCAAGCAAAAUGGGCU	
	GUCCCGACAACACGAACAGAUGACAAGUUGCGAAUGG	
	AGACAUGCUUCCAGCAGGCGUGUAAAGGUAAAAUCCA	
	AGCACUCUGCGAGAAUCCCGAGUGGGUACCAUUGAAG	
	GAUAACAGGAUUCCUUCAUACGGGGUCCUGUCUGUUG	
	AUCUGAGUCUGACGGUUGAGCUUAAAAUCAAAAUUG	
	CUUCGGGAUUCGGGCCAUUGAUCACACACGGCUCAGG	
	GAUGGACCUAUACAAAUCCAACUGCAACAAUGUGUAU	
	UGGCUGACUAUUCCGCCAAUGAGAAAUCUAGCCUUAG	
	GCGUAAUCAACACAUUGGAGUGGAUACCGAGAUUCA	
	AGGUUAGUCCCAACCUCUUCACUGUCCCAAUUAAGGA	
	AGCAGGCGAAGACUGCCAUGCCCCAACAUACCUACCU	
	GCGGAGGUGGACGGUGAUGUCAAACUCAGUUCCAACC	
	UGGUGAUUCUACCUGGUCAAGAUCUCCAAUAUGUUU	
	UGGCAACCUACGAUACCUCCAGGGUUGAGCAUGCUGU	
	GGUUUAUUACGUUUACAGCCCAAGCCGCUCAUUUUCU	
	UACUUUUAUCCUUUUAGGUUGCCUAUAAAGGGGGUC	
	CCAAUCGAACUACAAGUGGAAUGCUUCACAUGGGAUC	
	AAAAACUCUGGUGCCGUCACUUCUGUGUGCUUGCGGA	
	CUCAGAAUCCGGUGGACUUAUCACUCACUCUGGGAUG	
	GUGGGCAUGGGAGUCAGCUGCACAGCUACCCGGGAAG	
	AUGGAACCAAUCGCAGAUAA	
GC_H_MEASLES_B3 mRNA Sequence (assumes T100 Tail) Sequence Length: 2126	G*GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAA	77
	UAUAAGAGCCACCAUGUCACCGCAACGAGACCGGAUA	
	AAUGCCUUCUACAAAGAUAACCCUUAUCCCAAGGGAA	
	GUAGGAUAGUUAUUAACAGAGAACAUCUUAUGAUUG	
	ACAGACCCUAUGUUCUGCUGGCUGUUCUGUUCGUCAU	
	GUUUCUGAGCUUGAUCGGAUUGCUGGCAAUUGCAGG	
	CAUUAGACUUCAUCGGGCAGCCAUCUACACCGCGGAG	
	AUCCAUAAAAGCCUCAGUACCAAUCUGGAUGUGACUA	
	ACUCCAUCGAGCAUCAGGUCAAGGACGUGCUGACACC	
	ACUCUUUAAAAUCAUCGGGGAUGAAGUGGGCCUGAG	
	AACACCUCAGAGAUUCACUGACCUAGUGAAAUUCAUC	
	UCGGACAAGAUUAAAUUCCUUAAUCCGGAUAGGGAG	
	UACGACUUCAGAGAUCUCACUUGGUGCAUCAACCCGC	
	CAGAGAGGAUCAAACUAGAUUAUGAUCAAUACUGUG	
	CAGAUGUGGCUGCUGAAGAGCUCAUGAAUGCAUUGG	
	UGAACUCAACUCUACUGGAGACCAGAACAACCACUCA	
	GUUCCUAGCUGUCUCAAAGGGAAACUGCUCAGGGCCC	
	ACUACAAUCAGAGGUCAAUUCUCAAACAUGUCGCUGU	
	CCUUGUUGGACUUGUACUUAGGUCGAGGUUACAAUG	
	UGUCAUCUAUAGUCACUAUGACAUCCCAGGGAAUGUA	
	UGGGGGAACCUACCUAGUUGAAAAGCCUAAUCUGAAC	
	AGCAAAGGGUCAGAGUUGUCACAACUGAGCAUGUACC	
	GAGUGUUUGAAGUAGGUGUGAUCAGAAACCCGGGUU	
	UGGGGGCUCCGGUGUUCCAUAUGACAAACUAUUUUG	
	AGCAACCAGUCAGUAAUGGUCUCGGCAACUGUAUGGU	
	GGCUUUGGGGGAGCUCAAACUCGCAGCCCUUUGUCAC	
	GGGGACGAUUCUAUCAUAAUUCCCUAUCAGGGAUCAG	
	GGAAAGGUGUCAGCUUCCAGCUCGUCAAGCUGGGUGU	
	CUGGAAAUCCCCAACCGACAUGCAAUCCUGGGUCCCC	
	UUAUCAACGGAUGAUCCAGUGGUAGACAGGCUUUACC	
	UCUCAUCUCACAGAGGUGUCAUCGCUGACAAUCAAGC	
	AAAAUGGGCUGUCCCGACAACACGAACAGAUGACAAG	
	UUGCGAAUGGAGACAUGCUUCCAGCAGGCGUGUAAA	
	GGUAAAAUCCAAGCACUCUGCGAGAAUCCCGAGUGGG	
	UACCAUUGAAGGAUAACAGGAUUCCUUCAUACGGGG	
	UCCUGUCUGUUGAUCUGAGUCUGACGGUUGAGCUUA	
	AAAUCAAAAUUGCUUCGGGAUUCGGGCCAUUGAUCAC	
	ACACGGCUCAGGGAUGGACCUAUACAAAUCCAACUGC	
	AACAAUGUGUAUUGGCUGACUAUUCCGCCAAUGAGA	

TABLE 13-continued

MeV Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
	AAUCUAGCCUUAGGCGUAAUCAACACAUUGGAGUGG	
	AUACCGAGAUUCAAGGUUAGUCCCAACCUCUUCACUG	
	UCCCAAUUAAGGAAGCAGGCGAAGACUGCCAUGCCCC	
	AACAUACCUACCUGCGGAGGUGGACGGUGAUGUCAAA	
	CUCAGUUCCAACCUGGUGAUUCUACCUGGUCAAGAUC	
	UCCAAUAUGUUUUGGCAACCUACGAUACCUCCAGGGU	
	UGAGCAUGCUGUGGUUUAUUACGUUUACAGCCCAAGC	
	CGCUCAUUUUCUUACUUUUAUCCUUUUAGGUUGCCUA	
	UAAAGGGGGUCCCAAUCGAACUACAAGUGGAAUGCU	
	UCACAUGGGAUCAAAAACUCUGGUGCCGUCACUUCUG	
	UGUGCUUGCGGACUCAGAAUCCGGUGGACUUAUCACU	
	CACUCUGGGAUGGUGGGCAUGGGAGUCAGCUGCACAG	
	CUACCCGGGAAGAUGGAACCAAUCGCAGAUAAUGAUA	
	AUAGGCUGGAGCCUCGGUGGCCAAGCUUCUUGCCCCU	
	UGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACCC	
	GUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCG	
	GCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAUCUAG	
GC_H_MEASLES_D8 Sequence, NT (5' UTR, ORF, 3' UTR) Sequence Length: 2065	UCAAGCUUUUGGACCCUCGUACAGAAGCUAAUACGAC	78
	UCACUAUAGGGAAAUAAGAGAGAAAAGAAGAGUAAG	
	AAGAAAUAUAAGAGCCACCAUGUCACCACAACGAGAC	
	CGGAUAAAUGCCUUCUACAAAGACAACCCCCAUCCUA	
	AGGGAAGUAGGAUAGUUAUUAACAGAGAACAUCUUA	
	UGAUUGAUAGACCUUAUGUUUUGCUGGCUGUUCUAU	
	UCGUCAUGUUUCUGAGCUUGAUCGGGUUGCUAGCCAU	
	UGCAGGCAUUAGACUUCAUCGGGCAGCCAUCUACACC	
	GCAGAGAUCCAUAAAAGCCUCAGCACCAAUCUGGAUG	
	UAACUAACUCAAUCGAGCAUCAGGUUAAGGACGUGCU	
	GACACCACUCUUCAAGAUCAUCGGUGAUGAAGUGGGC	
	UUGAGGACACCUCAGAGAUUCACUGACCUAGUGAAGU	
	UCAUCUCUGACAAGAUUAAAUUCCUUAAUCCGGACAG	
	GGAAUACGACUUCAGAGAUCUCACUUGGUGUAUCAAC	
	CCGCCAGAGAGAAUCAAAUUGGAUUAUGAUCAAUAC	
	UGUGCAGAUGUGGCUGCUGAAGAACUCAUGAAUGCA	
	UUGGUGAACUCAACUCUACUGGAGACCAGGGCAACCA	
	AUCAGUUCCUAGCUGUCUCAAAGGGAAACUGCUCAGG	
	GCCCACUACAAUCAGAGGCCAAUUCUCAAACAUGUCG	
	CUGUCCCUGUUGGACUUGUAUUUAAGUCGAGGUUAC	
	AAUGUGUCAUCUAUAGUCACUAUGACAUCCCAGGGAA	
	UGUACGGGGGAACUUACCUAGUGGAAAAGCCUAAUC	
	UGAGCAGCAAAGGGUCAGAGUUGUCACAACUGAGCA	
	UGCACCGAGUGUUUGAAGUAGGUGUUAUCAGAAAUC	
	CGGGUUUGGGGGCUCCGGUAUUCCAUAUGACAAACUA	
	UCUUGAGCAACCAGUCAGUAAUGAUUUCAGCAACUGC	
	AUGGUGGCUUUGGGGGAGCUCAAGUUCGCAGCCCUCU	
	GUCACAGGGAAGAUUCUAUCACAAUUCCCUAUCAGGG	
	AUCAGGGAAAGGUGUCAGCUUCCAGCUUGUCAAGCUA	
	GGUGUCUGGAAAUCCCCAACCGACAUGCAAUCCUGGG	
	UCCCCCUAUCAACGGAUGAUCCAGUGAUAGACAGGCU	
	UUACCUCUCAUCUCACAGAGGCGUUAUCGCUGACAAU	
	CAAGCAAAAUGGGCUGUCCCGACAACACGGACAGAUG	
	ACAAGUUGCGAAUGGAGACAUGCUUCCAGCAGGCGUG	
	UAAGGGUAAAAUCCAAGCACUUUGCGAGAAUCCCGAG	
	UGGACACCAUUGAAGGAUAACAGGAUUCCUUCAUACG	
	GGGUCUUGUCUGUUGAUCUGAGUCUGACAGUUGAGC	
	UUAAAAUCAAAAUUGUUUCAGGAUUCGGGCCAUUGA	
	UCACACACGGUUCAGGGAUGGACCUAUACAAAUCCAA	
	CCACAACAAUAUGUAUUGGCUGACUAUCCCGCCAAUG	
	AAGAACCUGGCCUUAGGUGUAAUCAACACAUUGGAG	
	UGGAUACCGAGAUUCAAGGUUAGUCCCAACCUCUUCA	
	CUGUUCCAAUUAAGGAAGCAGGCGAGGACUGCCAUGC	
	CCCAACAUACCUACCUGCGGAGGUGGAUGGUGAUGUC	
	AAACUCAGUUCCAAUCUGGUGAUUCUACCUGGUCAAG	
	AUCUCCAAUAUGUUCUGGCAACCUACGAUACUUCCAG	
	AGUUGAACAUGCUGUAGUUUAUUACGUUUACAGCCC	
	AAGCCGCUCAUUUUCUUACUUUUAUCCUUUUAGGUUG	
	CCUGUAAGGGGGGUCCCCAUUGAAUUACAAGUGGAA	
	UGCUUCACAUGGGACCAAAAACUCUGGUGCCGUCACU	
	UCUGUGUGCUUGCGGACUCAGAAUCUGGUGGACAUA	
	UCACUCACUCUGGGAUGGUGGGCAUGGGAGUCAGCUG	
	CACAGCCACUCGGGAAGAUGGAACCAGCCGCAGAUAG	
	UGAUAAUAGGCUGGAGCCUCGGUGGCCAAGCUUCUUG	
	CCCCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUG	

TABLE 13-continued

MeV Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
	CACCCGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGU GGGCGGC	
GC_H_MEASLES_D8 ORF Sequence, NT	AUGUCACCACAACGAGACCGGAUAAAUGCCUUCUACA AAGACAACCCCCAUCCUAAGGGAAGUAGGAUAGUUAU UAACAGAGAACAUCUUAUGAUUGAUAGACCUUAUGU UUUGCUGGCUGUUCUAUUCGUCAUGUUUCUGAGCUU GAUCGGGUUGCUAGCCAUUGCAGGCAUUAGACUUCAU CGGGCAGCCAUCUACACCGCAGAGAUCCAUAAAAGCC UCAGCACCAAUCUGGAUGUAACUAACUCAAUCGAGCA UCAGGUUAAGGACGUGCUGACACCACUCUUCAAGAUC AUCGGUGAUGAAGUGGGCUUGAGGACACCUCAGAGA UUCACUGACCUAGUGAAGUUCAUCUCUGACAAGAUUA AAUUCCUUAAUCCGGACAGGGAAUACGACUUCAGAGA UCUCACUUGGUGUAUCAACCCGCCAGAGAGAAUCAAA UUGGAUUAUGAUCAAUACUGUGCAGAUGUGGCUGCU GAAGAACUCAUGAAUGCAUUGGUGAACUCAACUCUAC UGGAGACCAGGGCAACCAAUCAGUUCCUAGCUGUCUC AAAGGGAAACUGCUCAGGGCCCACUACAAUCAGAGGC CAAUUCUCAAACAUGUCGCUGUCCCUGUUGGACUUGU AUUUAAGUCGAGGUUACAAUGUGUCAUCUAUAGUCA CUAUGACAUCCCAGGGAAUGUACGGGGGAACUUACCU AGUGGAAAAGCCUAAUCUGAGCAGCAAAGGGUCAGA GUUGUCACAACUGAGCAUGCACCGAGUGUUUGAAGU AGGUGUUAUCAGAAAUCCGGGUUUGGGGGCUCCGGU AUUCCAUAUGACAAACUAUCUUGAGCAACCAGUCAGU AAUGAUUUCAGCAACUGCAUGGUGGCUUUGGGGGAG CUCAAGUUCGCAGCCCUCUGUCACAGGGAAGAUUCUA UCACAAUUCCCUAUCAGGGAUCAGGGAAAGGUGUCAG CUUCCAGCUUGUCAAGCUAGGUGUCUGGAAAUCCCCA ACCGACAUGCAAUCCUGGGUCCCCCUAUCAACGGAUG AUCCAGUGAUAGACAGGCUUUACCUCUCAUCUCACAG AGGCGUUAUCGCUGACAAUCAAGCAAAAUGGGCUGUC CCGACAACACGGACAGAUGACAAGUUGCGAAUGGAGA CAUGCUUCCAGCAGGCGUGUAAGGGUAAAAUCCAAGC ACUUUGCGAGAAUCCCGAGUGGACACCAUUGAAGGAU AACAGGAUUCCUUCAUACGGGGUCUUGUCUGUUGAUC UGAGUCUGACAGUUGAGCUUAAAAUCAAAAUUGUUU CAGGAUUCGGGCCAUUGAUCACACACGGUUCAGGGAU GGACCUAUACAAAUCCAACCACAACAAUAUGUAUUGG CUGACUAUCCCGCCAAUGAAGAACCUGGCCUUAGGUG UAAUCAACACAUUGGAGUGGAUACCGAGAUUCAAGG UUAGUCCCAACCUCUUCACUGUUCCAAUUAAGGAAGC AGGCGAGGACUGCCAUGCCCCAACAUACCUACCUGCG GAGGUGGAUGGUGAUGUCAAACUCAGUUCCAAUCUG GUGAUUCUACCUGGUCAAGAUCUCCAAUAUGUUCUGG CAACCUACGAUACUUCCAGAGUUGAACAUGCUGUAGU UUAUUACGUUUACAGCCCAAGCCGCUCAUUUUCUUAC UUUUAUCCUUUUAGGUUGCCUGUAAGGGGGGUCCCCA UUGAAUUACAAGUGGAAUGCUUCACAUGGGACCAAA AACUCUGGUGCCGUCACUUCUGUGUGCUUGCGGACUC AGAAUCUGGUGGACAUAUCACUCACUCUGGGAUGGU GGGCAUGGGAGUCAGCUGCACAGCCACUCGGGAAGAU GGAACCAGCCGCAGAUAG	79
GC_H_MEASLES_D8 mRNA Sequence (assumes T100 tail) Sequence Length: 2126	G*GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAA UAUAAGAGCCACCAUGUCACCACAACGAGACCGGAUA AAUGCCUUCUACAAAGACAACCCCCAUCCUAAGGGAA GUAGGAUAGUUAUUAACAGAGAACAUCUUAUGAUUG AUAGACCUUAUGUUUUGCUGGCUGUUCUAUUCGUCA UGUUUCUGAGCUUGAUCGGGUUGCUAGCCAUUGCAG GCAUUAGACUUCAUCGGGCAGCCAUCUACACCGCAGA GAUCCAUAAAAGCCUCAGCACCAAUCUGGAUGUAACU AACUCAAUCGAGCAUCAGGUUAAGGACGUGCUGACAC CACUCUUCAAGAUCAUCGGUGAUGAAGUGGGCUUGA GGACACCUCAGAGAUUCACUGACCUAGUGAAGUUCAU CUCUGACAAGAUUAAAUUCCUUAAUCCGGACAGGGAA UACGACUUCAGAGAUCUCACUUGGUGUAUCAACCCGC CAGAGAGAAUCAAAUUGGAUUAUGAUCAAUACUGUG CAGAUGUGGCUGCUGAAGAACUCAUGAAUGCAUUGG UGAACUCAACUCUACUGGAGACCAGGGCAACCAAUCA GUUCCUAGCUGUCUCAAAGGGAAACUGCUCAGGGCCC ACUACAAUCAGAGGCCAAUUCUCAAACAUGUCGCUGU CCCUGUUGGACUUGUAUUUAAGUCGAGGUUACAAUG UGUCAUCUAUAGUCACUAUGACAUCCCAGGGAAUGUA	80

TABLE 13-continued

MeV Nucleic Acid Sequences

Description	Sequence	SEQ ID NO:
	CGGGGGAACUUACCUAGUGGAAAAGCCUAAUCUGAGC	
	AGCAAAGGGUCAGAGUUGUCACAACUGAGCAUGCACC	
	GAGUGUUUGAAGUAGGUGUUAUCAGAAAUCCGGGUU	
	UGGGGGCUCCGGUAUUCCAUAUGACAAACUAUCUUGA	
	GCAACCAGUCAGUAAUGAUUUCAGCAACUGCAUGGUG	
	GCUUUGGGGGAGCUCAAGUUCGCAGCCCUCUGUCACA	
	GGGAAGAUUCUAUCACAAUUCCCUAUCAGGGAUCAGG	
	GAAAGGUGUCAGCUUCCAGCUUGUCAAGCUAGGUGUC	
	UGGAAAUCCCCAACCGACAUGCAAUCCUGGGUCCCCC	
	UAUCAACGGAUGAUCCAGUGAUAGACAGGCUUUACCU	
	CUCAUCUCACAGAGGCGUUAUCGCUGACAAUCAAGCA	
	AAAUGGGCUGUCCCGACAACACGGACAGAUGACAAGU	
	UGCGAAUGGAGACAUGCUUCCAGCAGGCGUGUAAGG	
	GUAAAAUCCAAGCACUUUGCGAGAAUCCCGAGUGGAC	
	ACCAUUGAAGGAUAACAGGAUUCCUUCAUACGGGGUC	
	UUGUCUGUUGAUCUGAGUCUGACAGUUGAGCUUAAA	
	AUCAAAAUUGUUUCAGGAUUCGGGCCAUUGAUCACAC	
	ACGGUUCAGGGAUGGACCUAUACAAAUCCAACCACAA	
	CAAUAUGUAUUGGCUGACUAUCCCGCCAAUGAAGAAC	
	CUGGCCUUAGGUGUAAUCAACACAUUGGAGUGGAUA	
	CCGAGAUUCAAGGUUAGUCCCAACCUCUUCACUGUUC	
	CAAUUAAGGAAGCAGGCGAGGACUGCCAUGCCCCAAC	
	AUACCUACCUGCGGAGGUGGAUGGUGAUGUCAAACUC	
	AGUUCCAAUCUGGUGAUUCUACCUGGUCAAGAUCUCC	
	AAUAUGUUCUGGCAACCUACGAUACUUCCAGAGUUGA	
	ACAUGCUGUAGUUUAUUACGUUUACAGCCCAAGCCGC	
	UCAUUUUCUUACUUUUAUCCUUUUAGGUUGCCUGUA	
	AGGGGGGUCCCCAUUGAAUUACAAGUGGAAUGCUUC	
	ACAUGGGACCAAAAACUCUGGUGCCGUCACUUCUGUG	
	UGCUUGCGGACUCAGAAUCUGGUGGACAUAUCACUCA	
	CUCUGGGAUGGUGGGCAUGGGAGUCAGCUGCACAGCC	
	ACUCGGGAAGAUGGAACCAGCCGCAGAUAGUGAUAA	
	UAGGCUGGAGCCUCGGUGGCCAAGCUUCUUGCCCCUU	
	GGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACCCG	
	UACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG	
	CAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAUCUAG	

TABLE 14

MeV Amino Acid Sequences

Description	Sequence	SEQ ID NO:
GC_F_MEASLES_B3.1 ORF Sequence, AA	MGLKVNVSAVFMAVLLTLQTPAGQIHWGNLSKIGVV GIGSASYKVMTRSSHQSLVIKLMPNITLLNNCTRVEIA EYRRLLRTVLEPIRDALNAMTQNIRPVQSVASSRRHK RFAGVVLAGAALGVATAAQITAGIALHRSMLNSQAID NLRASLETTNQAIEAIRQAGQEMILAVQGVQDYINNE LIPSMNQLSCDLIGQKLGLKLLRYYTEILSLFGPSLRDP ISAEISIQALSYALGGDINKVLEKLGYSGGDLLGILESR GIKARITHVDTESYFIVLSIAYPTLSEIKGVIVHRLEGVS YNIGSQEWYTTVPKYVATQGYLISNFDESSCTFMPEG TVCSQNALYPMSPLLQECLRGSTKSCARTLVSGSFGN RFILSQGNLIANCASILCKCYTTGTIINQDPDKILTYIAA DRCPVVEVNGVTIQVGSRRYPDAVYLHRIDLGPPISLE RLDVGTNLGNAIAKLEDAKELLESSDQILRSMKGLSST SIVYILIAVCLGGLIGIPTLICCCRGRCNKKGEQVGMSR PGLKPDLTGTSKSYVRSL*	47
GC_F_MEASLES_D8 ORF Sequence, AA	MGLKVNVSVIFMAVLLTLQTPTGQIHWGNLSKIGVVG VGSASYKVMTRSSHQSLVIKLMPNITLLNNCTRVGIAE YRRLLRTVLEPIRDALNAMTQNIRPVQSVASSRRHKR FAGVVLAGAALGVATAAQITAGIALHQSMLNSQAIDN LRASLETTNQAIEAIRQAGQEMILAVQGVQDYINNELI PSMNQLSCDLIGQKLGLKLLRYYTEILSLFGPSLRDPIS AEISIQALSYALGGDINKVLEKLGYSGGDLLGILESRGI KARITHVDTESYFIVLSIAYPTLSEIKGVIVHRLEGVSY NIGSQEWYTTVPKYVATQGYLISNFDESSCTFMPEGT VCSQNALYPMSPLLQECLRGSTKSCARTLVSGSFGNR	48

TABLE 14-continued

MeV Amino Acid Sequences

Description	Sequence	SEQ ID NO:
	FILSQGNLIANCASILCKCYTTGTIINQDPDKILTYIAAD HCPVVEVNGVTIQVGSRRYPDAVYLHRIDLGPPISLER LDVGTNLGNAIAKLEDAKELLESSDQILRSMKGLSSTS IVYILIAVCLGGLIGIPALICCCRGRCNKKGEQVGMSRP GLKPDLTGTSKSYVRSL*	
GC_H_MEASLES_B3 ORF Sequence, AA	MSPQRDRINAFYKDNPYPKGSRIVINREHLMIDRPYVL LAVLFVMFLSLIGLLAIAGIRLHRAAIYTAEIHKSLSTN LDVTNSIEHQVKDVLTPLFKIIGDEVGLRTPQRFTDLV KFISDKIKFLNPDREYDFRDLTWCINPPERIKLDYDQY CADVAAEELMNALVNSTLLETRTTTQFLAVSKGNCS GPTTIRGQFSNMSLSLLDLYLGRGYNVSSIVTMTSQG MYGGTYLVEKPNLNSKGSELSQLSMYRVFEVGVIRNP GLGAPVFHMTNYFEQPVSNGLGNCMVALGELKLAAL CHGDDSIIIPYQGSGKGVSFQLVKLGVWKSPTDMQSW VPLSTDDPVVDRLYLSSHRGVIADNQAKWAVPTTRT DDKLRMETCFQQACKGKIQALCENPEWVPLKDNRIPS YGVLSVDLSLTVELKIKIASGFGPLITHGSGMDLYKSN CNNVYWLTIPPMRNLALGVINTLEWIPRFKVSPNLFTV PIKEAGEDCHAPTYLPAEVDGDVKLSSNLVILPGQDL QYVLATYDTSRVEHAVVYYVYSPSRSFSYFYPFRLPIK GVPIELQVECFTWDQKLWCRHFCVLADSESGGLITHS GMVGMGVSCTATREDGTNRR*	49
GC_H_MEASLES_D8 ORF Sequence, AA	MSPQRDRINAFYKDNPHPKGSRIVINREHLMIDRPYVL LAVLFVMFLSLIGLLAIAGIRLHRAAIYTAEIHKSLSTN LDVTNSIEHQVKDVLTPLFKIIGDEVGLRTPQRFTDLV KFISDKIKFLNPDREYDFRDLTWCINPPERIKLDYDQY CADVAAEELMNALVNSTLLETRATNQFLAVSKGNCS GPTTIRGQFSNMSLSLLDLYLSRGYNVSSIVTMTSQGM YGGTYLVEKPNLSSKGSELSQLSMHRVFEVGVIRNPG LGAPVFHMTNYLEQPVSNDFSNCMVALGELKFAALC HREDSITIPYQGSGKGVSFQLVKLGVWKSPTDMQSW VPLSTDDPVIDRLYLSSHRGVIADNQAKWAVPTTRTD DKLRMETCFQQACKGKIQALCENPEWTPLKDNRIPSY GVLSVDLSLTVELKIKIVSGFGPLITHGSGMDLYKSNH NNMYWLTIPPMKNLALGVINTLEWIPRFKVSPNLFTV PIKEAGEDCHAPTYLPAEVDGDVKLSSNLVILPGQDL QYVLATYDTSRVEHAVVYYVYSPSRSFSYFYPFRLPV RGVPIELQVECFTWDQKLWCRHFCVLADSESGGHITH SGMVGMGVSCTATREDGTSRR*	50

TABLE 15

MeV NCBI Accession Numbers (Amino Acid Sequences)

Type	Virus Name	GenBank Accession
hemagglutinin	hemagglutinin [Measles virus strain Moraten]	AAF85673.1
hemagglutinin	hemagglutinin [Measles virus strain Rubeovax]	AAF85689.1
hemagglutinin	hemagglutinin [Measles virus]	AAF89824.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAA91369.1
hemagglutinin	hemagglutinin [Measles virus]	BAJ23068.1
hemagglutinin	hemagglutinin protein [Measles virus]	BAB39848.1
hemagglutinin	hemagglutinin [Measles virus]	AAA50551.1
hemagglutinin	RecName: Full = Hemagglutinin glycoprotein	P08362.1
hemagglutinin	hemagglutinin [Measles virus]	AAB63802.1
hemagglutinin	hemagglutinin [Measles virus]	AAA56650.1
hemagglutinin	hemagglutinin [Measles virus]	AAA56642.1
hemagglutinin	hemagglutinin [Measles virus]	AAA74936.1
hemagglutinin	hemagglutinin protein [Measles virus]	BAH56665.1
hemagglutinin	hemagglutinin [Measles virus]	ACC86105.1
hemagglutinin	hemagglutinin [Measles virus strain Edmonston-Zagreb]	AAF85697.1
hemagglutinin	hemagglutinin [Measles virus]	AAR89413.1
hemagglutinin	hemagglutinin [Measles virus]	AAA56653.1
hemagglutinin	RecName: Full = Hemagglutinin glycoprotein	P35971.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94916.1
hemagglutinin	hemagglutinin [Measles virus]	AAC03036.1
hemagglutinin	hemagglutinin [Measles virus]	AAF85681.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94927.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94925.1
hemagglutinin	hemagglutinin protein [Measles virus]	BAB39835.1

TABLE 15-continued

MeV NCBI Accession Numbers (Amino Acid Sequences)

Type	Virus Name	GenBank Accession
hemagglutinin	Hemagglutinin [Measles virus]	CAB94931.1
hemagglutinin	hemagglutinin [Measles virus genotype A]	AFO84712.1
hemagglutinin	hemagglutinin [Measles virus]	AAA56639.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94926.1
hemagglutinin	hemagglutinin protein [Measles virus]	BAB39836.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94929.1
hemagglutinin	RecName: Full = Hemagglutinin glycoprotein	P06830.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94928.1
hemagglutinin	hemagglutinin protein [Measles virus]	BAB39837.1
hemagglutinin	hemagglutinin [Measles virus]	AAA74935.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43780.1
hemagglutinin	hemagglutinin [Measles virus]	BAA09952.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43815.1
hemagglutinin	hemagglutinin [Measles virus]	AAF28390.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94923.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43785.1
hemagglutinin	hemagglutinin [Measles virus]	ABD34001.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43782.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43781.1
hemagglutinin	hemagglutinin [Measles virus]	BAH22353.1
hemagglutinin	hemagglutinin [Measles virus]	AAC35878.2
hemagglutinin	hemagglutinin protein [Measles virus]	AAL86996.1
hemagglutinin	hemagglutinin [Measles virus]	CAA76066.2
hemagglutinin	hemagglutinin [Measles virus]	AAA46428.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43803.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94918.1
hemagglutinin	hemagglutinin [Measles virus]	AAF72162.1
hemagglutinin	hemagglutinin [Measles virus]	AAM70154.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43776.1
hemagglutinin	hemagglutinin [Measles virus genotype D4]	ACT78395.1
hemagglutinin	hemagglutinin [Measles virus genotype D7]	AAL02030.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43789.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43774.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94920.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94922.1
hemagglutinin	hemagglutinin [Measles virus]	ABB59491.1
hemagglutinin	hemagglutinin protein [Measles virus]	BAB39843.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43804.1
hemagglutinin	hemagglutinin [Measles virus]	AAX52048.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94930.1
hemagglutinin	hemagglutinin [Measles virus]	AAA74526.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43814.1
hemagglutinin	hemagglutinin [Measles virus]	ABB59493.1
hemagglutinin	hemagglutinin [Measles virus genotype D4]	AAL02019.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94919.1
hemagglutinin	hemagglutinin protein [Measles virus]	AAL86997.1
hemagglutinin	hemagglutinin [Measles virus genotype C2]	AAL02017.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43769.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43808.1
hemagglutinin	hemagglutinin [Measles virus]	BAO97032.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43805.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43777.1
hemagglutinin	hemagglutinin [Measles virus]	AAL67793.1
hemagglutinin	hemagglutinin [Measles virus]	AAF89816.1
hemagglutinin	hemagglutinin [Measles virus genotype D4]	AAL02020.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43786.1
hemagglutinin	hemagglutinin protein [Measles virus strain MVi/New Jersey.USA/45.05]	AEP40452.1
hemagglutinin	hemagglutinin [Measles virus]	AAA74531.1
hemagglutinin	hemagglutinin [Measles virus]	AAB63800.1
hemagglutinin	hemagglutinin [Measles virus]	AAO21711.1
hemagglutinin	hemagglutinin [Measles virus genotype D8]	ALE27189.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43810.1
hemagglutinin	hemagglutinin [Measles virus]	AAF89817.1
hemagglutinin	hemagglutinin [Measles virus genotype D6]	AAL02022.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43800.1
hemagglutinin	hemagglutinin protein [Measles virus genotype B3]	AGA17219.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43770.1
hemagglutinin	hemagglutinin protein [Measles virus strain MVi/Texas.USA/4.07]	AEP40444.1
hemagglutinin	hemagglutinin [Measles virus]	AAX52047.1
hemagglutinin	hemagglutinin [Measles virus]	AAB63794.1
hemagglutinin	hemagglutinin [Measles virus]	AAB63796.1
hemagglutinin	hemagglutinin [Measles virus]	AAA74528.1
hemagglutinin	hemagglutinin [Measles virus]	AAB63774.1
hemagglutinin	hemagglutinin [Measles virus]	AAB63795.1

TABLE 15-continued

MeV NCBI Accession Numbers (Amino Acid Sequences)

Type	Virus Name	GenBank Accession
hemagglutinin	hemagglutinin [Measles virus]	AAA74519.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43778.1
fusion protein	fusion protein [Measles virus strain Moraten]	AAF85672.1
fasion protein	fusion protein [Measles virus]	AAA56645.1
fusion protein	fusion protein [Measles virus strain Rubeovax]	AAF85688.1
fusion protein	fusion protein [Measles virus]	AAF85680.1
fusion protein	fusion protein [Measles virus]	AEF30359.1
fusion protein	fusion protein [Measles virus]	BAA09957.1
fusion protein	fusion protein [Measles virus]	AAV84957.1
fusion protein	fusion protein [Measles virus MeV-eGFP_Edm-tag]	AII16636.1
fusion protein	fusion protein [Measles virus]	ABY58018.1
fusion protein	fusion protein [Measles virus]	BAA19838.1
fusion protein	fusion protein [Measles virus]	AAA56641.1
fusion protein	F protein [Measles virus]	ABK40529.1
fusion protein	fusion protein [Measles virus]	AAA56652.1
fusion protein	fusion protein [Measles virus]	ABY58017.1
fusion protein	fusion protein [Measles virus]	ABB71645.1
fusion protein	fusion protein [Measles virus]	NP_056922.1
fusion protein	fusion protein [Measles virus strain AIK-C]	AAF85664.1
fusion protein	fusion protein [Measles virus]	BAB60865.1
fusion protein	fusion protein [Measles virus]	BAA09950.1
fusion protein	fusion protein [Measles virus strain MVi/New York.USA/26.09/3]	AEP40403.1
fusion protein	fusion protein [Measles virus]	AAA74934.1
fusion protein	fusion protein [Measles virus]	CAB38075.1
fusion protein	fusion protein [Measles virus strain MVi/Texas.USA/4.07]	AEP40443.1
fusion protein	fusion protein [Measles virus]	AAF02695.1
fusion protein	fusion protein [Measles virus]	AAF02696.1
fusion protein	fusion protein [Measles virus]	AAT99301.1
fusion protein	fusion protein [Measles virus]	ABB71661.1
fusion protein	fusion protein [Measles virus]	BAK08874.1
fusion protein	fusion protein [Measles virus]	AAF02697.1
fusion protein	fusion protein [Measles virus genotype D4]	AFY12704.1
fusion protein	fusion protein [Measles virus strain MVi/California.USA/16.03]	AEP40467.1
fusion protein	fusion protein [Measles virus genotype D8]	AHN07989.1
fusion protein	fusion protein [Measles virus]	AAA46421.1
fusion protein	fusion protein [Measles virus]	AAA56638.1
fusion protein	fusion protein [Measles virus strain MVi/Virginia.USA/15.09]	AEP40419.1
fusion protein	fusion protein [Measles virus genotype D8]	ALE27200.1
fusion protein	fusion protein [Measles virus genotype D8]	AFY12695.1
fusion protein	fusion protein [Measles virus genotype D8]	ALE27248.1
fusion protein	fusion protein [Measles virus genotype D8]	ALE27224.1
fusion protein	fusion protein [Measles virus]	AAT99300.1
fusion protein	fusion protein [Measles virus]	BAH96592.1
fusion protein	fusion protein [Measles virus strain MVi/California.USA/8.04]	AEP40459.1
fusion protein	fusion protein [Measles virus genotype D8]	AIG94081.1
fusion protein	fusion protein [Measles virus]	BAA09951.1
fusion protein	fusion protein [Measles virus genotype D8]	ALE27194.1
fusion protein	fusion protein [Measles virus]	BAA33871.1
fusion protein	fusion protein [Measles virus strain MVi/Washington.USA/18.08/1]	AEP40427.1
fusion protein	fusion protein [Measles virus]	ABY21182.1
fusion protein	fusion protein [Measles virus genotype D8]	ALE27284.1
fusion protein	fusion protein [Measles virus]	ACA09725.1
fusion protein	fusion protein [Measles virus genotype D8]	ALE27314.1
fusion protein	fusion protein [Measles virus genotype G3]	AFY12712.1
fusion protein	fusion protein [Measles virus genotype D8]	ALE27368.1
fusion protein	RecName: Full = Fusion glycoprotein F0; Contains: RecName: Full = Fusion glycoprotein F2; Contains: RecName: Full = Fusion glycoprotein F1; Flags: Precursor	P35973.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53713.1
	unnamed protein product [Measles virus]	CAA34588.1
fusion protein	fusion protein [Measles virus]	CAA76888.1
fusion protein	fusion protein [Measles virus genotype B3.1]	AIY55563.1
fusion protein	fusion protein [Measles virus]	ADO17330.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53703.1
fusion protein	fusion protein [Measles virus genotype B3]	AGA17208.1
fusion protein	fusion protein [Measles virus]	AAL29688.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53706.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53701.1
fusion protein	fusion protein [Measles virus genotype B3]	ALE27092.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53714.1

TABLE 15-continued

MeV NCBI Accession Numbers (Amino Acid Sequences)

Type	Virus Name	GenBank Accession
fusion protein	fusion protein [Measles virus genotype H1]	AIG53694.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53668.1
fusion protein	fusion protein [Measles virus]	ACC86094.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53670.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53707.1
fusion protein	fusion protein [Measles virus genotype B3]	AGA17216.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53671.1
fusion protein	fusion protein [Measles virus strain MVi/New Jersey.USA/45.05]	AEP40451.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53684.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53688.1
fusion protein	fusion protein [Measles virus genotype B3]	AGA17214.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53683.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53667.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53686.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53685.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53681.1
	unnamed protein product [Measles virus]	CAA34589.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53678.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53710.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53669.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53664.1
fusion protein	fusion protein [Measles virus]	AAA50547.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53679.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53709.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53672.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53697.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53689.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53676.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53675.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53663.1
fusion protein	fusion protein [Measles virus]	BAA19841.1
fusion protein	fusion protein [Measles virus]	AAF02701.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53680.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53674.1
C protein	C protein [Measles virus strain Moraten]	AAF85670.1
C protein	RecName: Full = Protein C	P03424.1
C protein	C protein [Measles virus]	ACN54404.1
C protein	C protein [Measles virus]	ACN54412.1
C protein	RecName: Full = Protein C	P35977.1
C protein	C protein [Measles virus]	AAF85678.1
C protein	C protein [Measles virus]	ABD33998.1
C protein	unnamed protein product [Measles virus]	CAA34586.1
C protein	C protein [Measles virus]	BAJ51786.1
C protein	C protein [Measles virus]	BAA33869.1
C protein	virulence factor [Measles virus]	ABO69700.1
C protein	C protein [Measles virus]	NP_056920.1
C protein	C protein [Measles virus]	ADO17333.1
C protein	C protein [Measles virus]	ACC86082.1
C protein	C protein [Measles virus]	BAA33875.1
C protein	C protein [Measles virus]	ABY21189.1
C protein	C protein [Measles virus]	BAE98296.1
C protein	C protein [Measles virus]	ADU17782.1
C protein	C protein [Measles virus strain MVi/Virginia.USA/15.09]	AEP40417.1
C protein	C protein [Measles virus]	ADU17814.1
C protein	C protein [Measles virus]	ADU17798.1
C protein	C protein [Measles virus genotype D4]	AFY12700.1
C protein	C protein [Measles virus]	ADU17784.1
C protein	C protein [Measles virus strain MVi/California.USA/16.03]	AEP40465.1
C protein	C protein [Measles virus]	ABB71643.1
C protein	C protein [Measles virus]	AEI91027.1
C protein	C protein [Measles virus]	ADU17874.1
C protein	C protein [Measles virus]	ADU17903.1
C protein	C protein [Measles virus]	CAA34579.1
C protein	C protein [Measles virus]	ADU17790.1
C protein	C protein [Measles virus]	ADU17800.1
C protein	C protein [Measles virus]	ABB71667.1
C protein	unnamed protein product [Measles virus]	CAA34572.1
C protein	C protein [Measles virus strain MVi/Arizona.USA/11.08/2]	AEP40433.1
C protein	C protein [Measles virus]	ADU17830.1
C protein	C protein [Measles virus]	ADU17947.1
C protein	C protein [Measles virus]	ADU17818.1
C protein	C protein [Measles virus strain	AEP40449.1

TABLE 15-continued

MeV NCBI Accession Numbers (Amino Acid Sequences)

Type	Virus Name	GenBank Accession
	MVi/New Jersey.USA/45.05]	
C protein	C protein [Measles virus strain MVi/Texas.USA/4.07]	AEP40441.1
C protein	C protein [Measles virus]	ADU17864.1
C protein	C protein [Measles virus]	ADU17838.1
C protein	C protein [Measles virus]	ADU17881.1
C protein	C protein [Measles virus strain MVi/Washington.USA/18.08/1]	AEP40425.1
C protein	C protein [Measles virus]	ADU17927.1
C protein	C protein [Measles virus]	ADU17953.1
C protein	C protein [Measles virus]	ADU17889.1
C protein	C protein [Measles virus]	ADU17963.1
C protein	C protein [Measles virus]	ADU17893.1
C protein	C protein [Measles virus]	ADU17820.1
C protein	C protein [Measles virus]	ABB71651.1
C protein	C protein [Measles virus]	ADU17786.1
C protein	C protein [Measles virus]	ADU17862.1
C protein	C protein [Measles virus]	ADU17923.1
C protein	C protein [Measles virus]	ADU17959.1
C protein	C protein [Measles virus]	ADU17951.1
C protein	C protein [Measles virus]	ADU17916.1
C protein	C protein [Measles virus]	ADU17957.1
C protein	C protein [Measles virus]	ADU17925.1
C protein	C protein [Measles virus]	ADU17901.1
C protein	C protein [Measles virus]	ADU17887.1
C protein	C protein [Measles virus]	ADU17832.1
C protein	C protein [Measles virus]	ADU17891.1
C protein	C protein [Measles virus]	ADU17961.1
C protein	C protein [Measles virus]	ADU17872.1
C protein	C protein [Measles virus]	ADU17929.1
C protein	C protein [Measles virus]	ADU17908.1
C protein	C protein [Measles virus]	ADU17910.1
C protein	C protein [Measles virus]	ADU17921.1
C protein	C protein [Measles virus]	ADU17824.1
C protein	C protein [Measles virus strain MVi/Pennsylvania.USA/20.09]	AEP40473.1
C protein	C protein [Measles virus]	ADU17828.1
C protein	C protein [Measles virus]	ADU17812.1
C protein	C protein [Measles virus genotype D8]	AFY12692.1
C protein	nonstructural C protein [Measles virus]	ABA59559.1
C protein	RecName: Full = Protein C	Q00794.1
C protein	nonstructural C protein [Measles virus]	ADO17934.1
C protein	nonstructural C protein [Measles virus]	ACJ66773.1
C protein	C protein [Measles virus genotype G3]	AFY12708.1
C protein	RecName: Full = Protein C	P26035.1
C protein	C protein [Measles virus]	BAA84128.1
nucleoprotein	RecName: Full = Nucleoprotein; AltName: Full = Nucleocapsid protein; Short = NP; Short = Protein N	Q77M43.1
nucleoprotein	nucleocapsid protein [Measles virus strain Rubeovax]	AAF85683.1
nucleoprotein	RecName: Full = Nucleoprotein; AltName: Full = Nucleocapsid protein; Short = NP; Short = Protein N	Q89933.1
nucleoprotein	nucleocapsid protein [Measles virus strain AIK-C]	AAF85659.1
nucleoprotein	nucleoprotein [Measles virus]	ABI54102.1
nucleoprotein	nucleoprotein [Measles virus]	AAA56643.1
nucleoprotein	nucleoprotein [Measles virus]	AAC03050.1
nucleoprotein	nucleoprotein [Measles virus]	AAA18990.1
nucleoprotein	nucleoprotein [Measles virus]	AAA56640.1
nucleoprotein	RecName: Full = Nucleoprotein; AltName: Full = Nucleocapsid protein; Short = NP; Short = Protein N	P35972.1
nucleoprotein	RecName: Full=Nucleoprotein; AltName: Full = Nucleocapsid protein; Short = NP; Short = Protein N	P10050.1
nucleoprotein	N protein [Measles virus]	BAB60956.1
nucleoprotein	RecName: Full = Nucleoprotein; AltName: Full = Nucleocapsid protein; Short = NP; Short = Protein N	B1AAA7.1
nucleoprotein	nucleoprotein [Measles virus]	AAA18991.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46894.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46871.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46872.1
nucleoprotein	nucleoprotein [Measles virus]	ABU49606.1
nucleoprotein	nucleocapsid protein [Measles virus]	AAA75494.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46883.1

TABLE 15-continued

MeV NCBI Accession Numbers (Amino Acid Sequences)

Type	Virus Name	GenBank Accession
nucleoprotein	nucleoprotein [Measles virus]	CAB46892.1
nucleoprotein	unnamed protein product [Measles virus]	CAA34584.1
nucleoprotein	nucleoprotein [Measles virus]	AAA18997.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46863.1
nucleoprotein	nucleoprotein [Measles virus]	AEF30352.1
nucleoprotein	nucleoprotein [Measles virus]	ABI54103.1
nucleoprotein	nucleocapsid protein [Measles virus]	AAA46433.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46902.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46873.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46906.1
nucleoprotein	nucleoprotein [Measles virus]	AAA74547.1
nucleoprotein	nucleoprotein [Measles virus]	AAA74537.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46862.1
nucleoprotein	nucleocapsid protein [Measles virus]	BAA09961.1
nucleoprotein	nucleoprotein [Measles virus]	AAO15875.1
nucleoprotein	nucleoprotein [Measles virus]	AAO15871.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46882.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60124.1
nucleoprotein	nucleoprotein [Measles virus]	ABI54104.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46869.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46880.1
nucleoprotein	nucleoprotein [Measles virus]	AAA74541.1
nucleoprotein	nucleocapsid protein [Measles virus strain MVi/New Jersey.USA/45.05]	AEP40446.1
nucleoprotein	nucleoprotein [Measles virus]	ABI54110.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46903.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46899.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46901.1
nucleoprotein	nucleocapsid protein [Measles virus]	ABB71640.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60113.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60114.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60116.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46895.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60121.1
nucleoprotein	nucleoprotein [Measles virus]	ABI54111.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46889.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46898.1
nucleoprotein	nucleoprotein [Measles virus genotype B3]	ALE27083.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60118.1
nucleoprotein	nucleocapsid protein [Measles virus]	CAA34570.1
nucleoprotein	nucleoprotein [Measles virus]	AAC29443.1
nucleoprotein	nucleocapsid protein [Measles virus strain MVi/Washington.USA/18.08/1]	AEP40422.1
nucleoprotein	nucleoprotein [Measles virus]	AAO15872.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46874.1
nucleoprotein	nucleoprotein [Measles virus]	AAA74550.1
nucleoprotein	nucleocapsid protein [Measles virus]	ABB71648.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46900.1
nucleoprotein	nucleoprotein [Measles virus]	BAH22440.1
nucleoprotein	nucleocapsid protein [Measles virus]	AAA46432.1
nucleoprotein	nucleocapsid protein [Measles virus]	BAA33867.1
nucleoprotein	nucleoprotein [Measles virus]	AAA74539.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60115.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60123.1
nucleoprotein	nucleocapsid protein [Measles virus]	ABB71664.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60125.1
nucleoprotein	nucleoprotein [Measles virus]	AAA74546.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46886.1
nucleoprotein	nucleoprotein [Measles virus]	BAH22350.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46867.1
nucleoprotein	nucleocapsid protein [Measles virus]	BAA09954.1
nucleoprotein	nucleoprotein [Measles virus]	AAO15873.1
nucleoprotein	nucleocapsid protein [Measles virus]	AEP95735.1
nucleoprotein	nucleoprotein [Measles virus]	AAL37726.1
nucleoprotein	nucleoprotein [Measles virus]	AAA74549.1
nucleoprotein	RecName: Full = Nucleoprotein; AltName: Full = Nucleocapsid protein; Short = NP; Short = Protein N	P26030.1
nucleoprotein	nucleoprotein [Measles virus ETH55/99]	AAK07777.1
nucleoprotein	nucleoprotein [Measles virus genotype B3]	AGA17238.1
nucleoprotein	nucleoprotein [Measles virus]	AEF30351.1
nucleoprotein	nucleoprotein [Measles virus genotype B3]	AGA17242.1
nucleoprotein	nucleoprotein [Measles virus ETH54/98]	AAK07776.1
nucleoprotein	nucleoprotein [Measles virus]	AAA74548.1
nucleoprotein	nucleoprotein [Measles virus]	AAA19221.1
nucleoprotein	nucleoprotein [Measles virus]	AAC03039.1

TABLE 15-continued

MeV NCBI Accession Numbers (Amino Acid Sequences)

Type	Virus Name	GenBank Accession
nucleoprotein	nucleoprotein [Measles virus]	AAA19223.1
nucleoprotein	nucleoprotein [Measles virus genotype B3]	AGA17241.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60122.1
nucleoprotein	nucleoprotein [Measles virus]	CAC34599.1
nucleoprotein	nucleoprotein [Measles virus]	AAC03042.1
nucleoprotein	nucleoprotein [Measles virus]	CAC34604.1
nucleoprotein	nucleoprotein [Measles virus]	AAA74544.1
nucleoprotein	nucleocapsid protein [Measles virus]	NP_056918.1
V Protein	RecName: Full = Non-structural protein V	Q9IC37.1
V Protein	RecName: Full = Non-structural protein V	Q9EMA9.1
V Protein	V protein [Measles virus]	ACN54411.1
V Protein	V protein [Measles virus]	ACN54403.1
V Protein	V protein [Measles virus]	AEP95742.1
V Protein	V protein [Measles virus strain MVi/Virginia.USA/15.09]	AEP40416.1
V Protein	V protein [Measles virus]	ADU17801.1
V Protein	V protein [Measles virus]	ADU17849.1
V Protein	V protein [Measles virus]	ABB71642.1
V Protein	V protein [Measles virus genotype D8]	AFY12693.1
V Protein	V protein [Measles virus]	YP_003873249.2
V Protein	V protein [Measles virus strain MVi/Arizona.USA/11.08/2]	AEP40432.1
V Protein	RecName: Full = Non-structural protein V	P26036.1
V Protein	V protein [Measles virus strain MVi/California.USA/16.03]	AEP40464.1
V Protein	V protein [Measles virus strain MVi/California.USA/8.04]	AEP40456.1
V Protein	V protein [Measles virus]	ABY21188.1
V Protein	V protein [Measles virus strain MVi/Washington.USA/18.08/1]	AEP40424.1
V Protein	V protein [Measles virus]	BAH96581.1
V Protein	V protein [Measles virus]	ABB71666.1
V Protein	RecName: Full = Non-structural protein V	P60168.1
V Protein	V protein [Measles virus]	BAH96589.1
V Protein	V protein [Measles virus]	ADU17954.1
V Protein	V protein [Measles virus strain MVi/New York.USA/26.09/3]	AEP40400.1
V Protein	V protein [Measles virus]	ABY21196.1
V Protein	virulence factor [Measles virus]	ABO69701.1
V Protein	V protein [Measles virus]	ABB71650.1
V Protein	V protein [Measles virus]	ACC86086.1
V Protein	V protein [Measles virus genotype D4]	AFY12702.1
V Protein	V protein [Measles virus strain MVi/New Jersey.USA/45.05]	AEP40448.1
V Protein	V protein [Measles virus]	BAE98295.1
V Protein	V protein [Measles virus]	ACC86083.1
V Protein	V protein [Measles virus]	ACU5139.1
V Protein	V protein [Measles virus]	ADO17334.1
V Protein	V protein [Measles virus]	ADU17930.1
V Protein	V protein [Measles virus genotype G3]	AFY12710.1
V Protein	V protein [Measles virus strain MVi/Pennsylvania.USA/20.09]	AEP40472.1
V Protein	phosphoprotein [Measles virus]	ADU17839.1
V Protein	V protein [Measles virus]	ADU17894.1
V Protein	V protein [Measles virus]	ACN50010.1
V Protein	V protein [Measles virus]	ADU17892.1
	unnamed protein product [Measles virus]	CAA34585.1
V Protein	V protein [Measles virus]	ABD33997.1

TABLE 16

Name	Sequence	SEQ ID NO:
	Flagellin Nucleic Acid Sequences	
NT (5' UTR, ORF, 3' UTR)	TCAAGCTTTTGGACCCTCGTACAGAAGCTAATACGACTCACTAT AGGGAAATAAGAGAGAAAAGAAGAGTAAGAAGAAATATAAG AGCCACCATGGCACAAGTCATTAATACAAACAGCCTGTCGCTG TTGACCCAGAATAACCTGAACAAATCCCAGTCCGCACTGGGCA CTGCTATCGAGCGTTTGTCTTCCGGTCTGCGTATCAACAGCGCG AAAGACGATGCGGCAGGACAGGCGATTGCTAACCGTTTTACCG CGAACATCAAAGGTCTGACTCAGGCTTCCCGTAACGCTAACGA	51

TABLE 16-continued

Name	Sequence	SEQ ID NO:
	CGGTATCTCCATTGCGCAGACCACTGAAGGCGCGCTGAACGAA	
	ATCAACAACAACCTGCAGCGTGTGCGTGAACTGGCGGTTCAGT	
	CTGCGAATGGTACTAACTCCCAGTCTGACCTCGACTCCATCCAG	
	GCTGAAATCACCCAGCGCCTGAACGAAATCGACCGTGTATCCG	
	GCCAGACTCAGTTCAACGGCGTGAAAGTCCTGGCGCAGGACAA	
	CACCCTGACCATCCAGGTTGGTGCCAACGACGGTGAAACTATC	
	GATATTGATTTAAAAGAAATCAGCTCTAAAACACTGGGACTTG	
	ATAAGCTTAATGTCCAAGATGCCTACACCCCGAAAGAAACTGC	
	TGTAACCGTTGATAAAACTACCTATAAAAATGGTACAGATCCT	
	ATTACAGCCCAGAGCAATACTGATATCCAAACTGCAATTGGCG	
	GTGGTGCAACGGGGGTTACTGGGGCTGATATCAAATTTAAAGA	
	TGGTCAATACTATTTAGATGTTAAAGGCGGTGCTTCTGCTGGTG	
	TTTATAAAGCCACTTATGATGAAACTACAAAGAAAGTTAATAT	
	TGATACGACTGATAAAACTCCGTTGGCAACTGCGGAAGCTACA	
	GCTATTCGGGGAACGGCCACTATAACCCACAACCAAATTGCTG	
	AAGTAACAAAAGAGGGTGTTGATACGACCACAGTTGCGGCTCA	
	ACTTGCTGCAGCAGGGGTTACTGGCGCCGATAAGGACAATACT	
	AGCCTTGTAAAACTATCGTTTGAGGATAAAAACGGTAAGGTTA	
	TTGATGGTGGCTATGCAGTGAAAATGGGCGACGATTTCTATGC	
	CGCTACATATGATGAGAAAACAGGTGCAATTACTGCTAAAACC	
	ACTACTTATACAGATGGTACTGGCGTTGCTCAAACTGGAGCTGT	
	GAAATTTGGTGGCGCAAATGGTAAATCTGAAGTTGTTACTGCT	
	ACCGATGGTAAGACTTACTTAGCAAGCGACCTTGACAAACATA	
	ACTTCAGAACAGGCGGTGAGCTTAAAGAGGTTAATACAGATAA	
	GACTGAAAACCCACTGCAGAAAATTGATGCTGCCTTGGCACAG	
	GTTGATACACTTCGTTCTGACCTGGGTGCGGTTCAGAACCGTTT	
	CAACTCCGCTATCACCAACCTGGGCAATACCGTAAATAACCTG	
	TCTTCTGCCCGTAGCCGTATCGAAGATTCCGACTACGCAACCGA	
	AGTCTCCAACATGTCTCGCGCGCAGATTCTGCAGCAGGCCGGT	
	ACCTCCGTTCTGGCGCAGGCGAACCAGGTTCCGCAAAACGTCC	
	TCTCTTTACTGCGTTGATAATAGGCTGGAGCCTCGGTGGCCATG	
	CTTCTTGCCCCTTGGGCCTCCCCCCAGCCCCTCCTCCCCTTCCTG	
	CACCCGTACCCCCGTGGTCTTTGAATAAAGTCTGAGTGGGCGGC	
ORF Sequence, NT	ATGGCACAAGTCATTAATACAAACAGCCTGTCGCTGTTGACCC	52
	AGAATAACCTGAACAAATCCCAGTCCGCACTGGGCACTGCTAT	
	CGAGCGTTTGTCTTCCGGTCTGCGTATCAACAGCGCGAAAGAC	
	GATGCGGCAGGACAGGCGATTGCTAACCGTTTTACCGCGAACA	
	TCAAAGGTCTGACTCAGGCTTCCCGTAACGCTAACGACGGTAT	
	CTCCATTGCGCAGACCACTGAAGGCGCGCTGAACGAAATCAAC	
	AACAACCTGCAGCGTGTGCGTGAACTGGCGGTTCAGTCTGCGA	
	ATGGTACTAACTCCCAGTCTGACCTCGACTCCATCCAGGCTGAA	
	ATCACCCAGCGCCTGAACGAAATCGACCGTGTATCCGGCCAGA	
	CTCAGTTCAACGGCGTGAAAGTCCTGGCGCAGGACAACACCCT	
	GACCATCCAGGTTGGTGCCAACGACGGTGAAACTATCGATATT	
	GATTTAAAAGAAATCAGCTCTAAAACACTGGGACTTGATAAGC	
	TTAATGTCCAAGATGCCTACACCCCGAAAGAAACTGCTGTAAC	
	CGTTGATAAAACTACCTATAAAAATGGTACAGATCCTATTACA	
	GCCCAGAGCAATACTGATATCCAAACTGCAATTGGCGGTGGTG	
	CAACGGGGGTTACTGGGGCTGATATCAAATTTAAAGATGGTCA	
	ATACTATTTAGATGTTAAAGGCGGTGCTTCTGCTGGTGTTTATA	
	AAGCCACTTATGATGAAACTACAAAGAAAGTTAATATTGATAC	
	GACTGATAAAACTCCGTTGGCAACTGCGGAAGCTACAGCTATT	
	CGGGGAACGGCCACTATAACCCACAACCAAATTGCTGAAGTAA	
	CAAAAGAGGGTGTTGATACGACCACAGTTGCGGCTCAACTTGC	
	TGCAGCAGGGGTTACTGGCGCCGATAAGGACAATACTAGCCTT	
	GTAAAACTATCGTTTGAGGATAAAAACGGTAAGGTTATTGATG	
	GTGGCTATGCAGTGAAAATGGGCGACGATTTCTATGCCGCTAC	
	ATATGATGAGAAAACAGGTGCAATTACTGCTAAAACCACTACT	
	TATACAGATGGTACTGGCGTTGCTCAAACTGGAGCTGTGAAAT	
	TTGGTGGCGCAAATGGTAAATCTGAAGTTGTTACTGCTACCGAT	
	GGTAAGACTTACTTAGCAAGCGACCTTGACAAACATAACTTCA	
	GAACAGGCGGTGAGCTTAAAGAGGTTAATACAGATAAGACTG	
	AAAACCCACTGCAGAAAATTGATGCTGCCTTGGCACAGGTTGA	
	TACACTTCGTTCTGACCTGGGTGCGGTTCAGAACCGTTTCAACT	
	CCGCTATCACCAACCTGGGCAATACCGTAAATAACCTGTCTTCT	
	GCCCGTAGCCGTATCGAAGATTCCGACTACGCAACCGAAGTCT	
	CCAACATGTCTCGCGCGCAGATTCTGCAGCAGGCCGGTACCTC	
	CGTTCTGGCGCAGGCGAACCAGGTTCCGCAAAACGTCCTCTCTT	
	TACTGCGT	
mRNA Sequence (assumes T100 tail)	G*GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUAA	53
	GAGCCACCAUGGCACAAGUCAUUAAUACAAACAGCCUGUCGC	
	UGUUGACCCAGAAUAACCUGAACAAAUCCCAGUCCGCACUGG	
	GCACUGCUAUCGAGCGUUUGUCUUCCGGUCUGCGUAUCAACA	
	GCGCGAAAGACGAUGCGGCAGGACAGGCGAUUGCUAACCGUU	
	UUACCGCGAACAUCAAAGGUCUGACUCAGGCUUCCCGUAACG	

TABLE 16-continued

Name	Sequence	SEQ ID NO:
	CUAACGACGGUAUCUCCAUUGCGCAGACCACUGAAGGCGCGC	
	UGAACGAAAUCAACAACAACCUGCAGCGUGUGCGUGAACUGG	
	CGGUUCAGUCUGCGAAUGGUACUAACUCCCAGUCUGACCUCG	
	ACUCCAUCCAGGCUGAAAUCACCCAGCGCCUGAACGAAAUCG	
	ACCGUGUAUCCGGCCAGACUCAGUUCAACGGCGUGAAAGUCC	
	UGGCGCAGGACAACACCCUGACCAUCCAGGUUGGUGCCAACG	
	ACGGUGAAACUAUCGAUAUUGAUUUAAAAGAAAUCAGCUCU	
	AAAACACUGGGACUUGAUAAGCUUAAUGUCCAAGAUGCCUAC	
	ACCCCGAAAGAAACUGCUGUAACCGUUGAUAAAACUACCUAU	
	AAAAAUGGUACAGAUCCUAUUACAGCCCAGAGCAAUACUGAU	
	AUCCAAACUGCAAUUGGCGGUGGUGCAACGGGGGUUACUGG	
	GGCUGAUAUCAAAUUUAAAGAUGGUCAAUACUAUUUAGAUG	
	UUAAAGGCGGUGCUUCUGCUGGUGUUUAUAAAGCCACUUAU	
	GAUGAAACUACAAAGAAAGUUAAUAUUGAUACGACUGAUAA	
	AACUCCGUUGGCAACUGCGGAAGCUACAGCUAUUCGGGGAAC	
	GGCCACUAUAACCCACAACCAAAUUGCUGAAGUAACAAAAGA	
	GGGUGUUGAUACGACCACAGUUGCGGCUCAACUUGCUGCAGC	
	AGGGGUUACUGGCGCCGAUAAGGACAAUACUAGCCUUGUAA	
	AACUAUCGUUUGAGGAUAAAAACGGUAAGGUUAUUGAUGGU	
	GGCUAUGCAGUGAAAAUGGGCGACGAUUUCUAUGCCGCUACA	
	UAUGAUGAGAAAACAGGUGCAAUUACUGCUAAAACCACUAC	
	UUAUACAGAUGGUACUGGCGUUGCUCAAACUGGAGCUGUGA	
	AAUUUGGUGGCGCAAAUGGUAAAUCUGAAGUUGUUACUGCU	
	ACCGAUGGUAAGACUUACUUAGCAAGCGACCUUGACAAACAU	
	AACUUCAGAACAGGCGGUGAGCUUAAAGAGGUUAAUACAGA	
	UAAGACUGAAAACCCACUGCAGAAAAUUGAUGCUGCCUUGGC	
	ACAGGUUGAUACACUUCGUUCUGACCUGGGUGCGGUUCAGAA	
	CCGUUUCAACUCCGCUAUCACCAACCUGGGCAAUACCGUAAA	
	UAACCUGUCUUCUGCCCGUAGCCGUAUCGAAGAUUCCGACUA	
	CGCAACCGAAGUCUCCAACAUGUCUCGCGCGCAGAUUCUGCA	
	GCAGGCCGGUACCUCCGUUCUGGCGCAGGCGAACCAGGUUCC	
	GCAAAACGUCCUCUCUUUACUGCGUUGAUAAUAGGCUGGAGC	
	CUCGGUGGCCAUGCUUCUUGCCCCUUGGGCCUCCCCCCAGCC	
	CCUCCUCCCCUUCCUGCACCCGUACCCCCGUGGUCUUUGAAU	
	AAAGUCUGAGUGGGCGGCAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAUCUAG	
	Flagellin mRNA Sequences	
NT (5' UTR, ORF, 3' UTR)	UCAAGCUUUUGGACCCUCGUACAGAAGCUAAUACGACUCACU AUAGGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGAGCCACCAUGGCACAAGUCAUUAAUACAAACAGCCUGUCG CUGUUGACCCAGAAUAACCUGAACAAAUCCCAGUCCGCACUG GGCACUGCUAUCGAGCGUUUGUCUUCCGGUCUGCGUAUCAAC AGCGCGAAAGACGAUGCGGCAGGACAGGCGAUUGCUAACCGU UUUACCGCGAACAUCAAAGGUCUGACUCAGGCUUCCCGUAAC GCUAACGACGGUAUCUCCAUUGCGCAGACCACUGAAGGCGCG CUGAACGAAAUCAACAACAACCUGCAGCGUGUGCGUGAACUG GCGGUUCAGUCUGCGAAUGGUACUAACUCCCAGUCUGACCUC GACUCCAUCCAGGCUGAAAUCACCCAGCGCCUGAACGAAAUC GACCGUGUAUCCGGCCAGACUCAGUUCAACGGCGUGAAAGUC CUGGCGCAGGACAACACCCUGACCAUCCAGGUUGGUGCCAAC GACGGUGAAACUAUCGAUAUUGAUUUAAAAGAAAUCAGCUC UAAAACACUGGGACUUGAUAAGCUUAAUGUCCAAGAUGCCU ACACCCCGAAAGAAACUGCUGUAACCGUUGAUAAAACUACCU AUAAAAAUGGUACAGAUCCUAUUACAGCCCAGAGCAAUACUG AUAUCCAAACUGCAAUUGGCGGUGGUGCAACGGGGGUUACU GGGGCUGAUAUCAAAUUUAAAGAUGGUCAAUACUAUUUAGA UGUUAAAGGCGGUGCUUCUGCUGGUGUUUAUAAAGCCACUU AUGAUGAAACUACAAAGAAAGUUAAUAUUGAUACGACUGAU AAAACUCCGUUGGCAACUGCGGAAGCUACAGCUAUUCGGGGA ACGGCCACUAUAACCCACAACCAAAUUGCUGAAGUAACAAAA GAGGGUGUUGAUACGACCACAGUUGCGGCUCAACUUGCUGCA GCAGGGGUUACUGGCGCCGAUAAGGACAAUACUAGCCUUGUA AAACUAUCGUUUGAGGAUAAAAACGGUAAGGUUAUUGAUGG UGGCUAUGCAGUGAAAAUGGGCGACGAUUUCUAUGCCGCUAC AUAUGAUGAGAAAACAGGUGCAAUUACUGCUAAAACCACUA CUUAUACAGAUGGUACUGGCGUUGCUCAAACUGGAGCUGUG AAAUUUGGUGGCGCAAAUGGUAAAUCUGAAGUUGUUACUGC UACCGAUGGUAAGACUUACUUAGCAAGCGACCUUGACAAACA UAACUUCAGAACAGGCGGUGAGCUUAAAGAGGUUAAUACAG AUAAGACUGAAAACCCACUGCAGAAAAUUGAUGCUGCCUUGG CACAGGUUGAUACACUUCGUUCUGACCUGGGUGCGGUUCAGA ACCGUUUCAACUCCGCUAUCACCAACCUGGGCAAUACCGUAA AUAACCUGUCUUCUGCCCGUAGCCGUAUCGAAGAUUCCGACU ACGCAACCGAAGUCUCCAACAUGUCUCGCGCGCAGAUUCUGC AGCAGGCCGGUACCUCCGUUCUGGCGCAGGCGAACCAGGUUC	81

TABLE 16-continued

Name	Sequence	SEQ ID NO:
	CGCAAAACGUCCUCUCUUUACUGCGUUGAUAAUAGGCUGGAG CCUCGGUGGCCAUGCUUCUUGCCCCUUGGGCCUCCCCCCAGC CCCUCCUCCCCUUCCUGCACCCGUACCCCCGUGGUCUUUGAA UAAAGUCUGAGUGGGCGGC	
ORF Sequence, NT	AUGGCACAAGUCAUUAAUACAAACAGCCUGUCGCUGUUGACC CAGAAUAACCUGAACAAAUCCCAGUCCGCACUGGGCACUGCU AUCGAGCGUUUGUCUUCCGGUCUGCGUAUCAACAGCGCGAAA GACGAUGCGGCAGGACAGGCGAUUGCUAACCGUUUUACCGCG AACAUCAAAGGUCUGACUCAGGCUUCCCGUAACGCUAACGAC GGUAUCUCCAUUGCGCAGACCACUGAAGGCGCGCUGAACGAA AUCAACAACAACCUGCAGCGUGUGCGUGAACUGGCGGUUCAG UCUGCGAAUGGUACUAACUCCCAGUCUGACCUCGACUCCAUC CAGGCUGAAAAUCACCCAGCGCCUGAACGAAAUCGACCGUGUA UCCGGCCAGACUCAGUUCAACGGCGUGAAAGUCCUGGCGCAG GACAACACCCUGACCAUCCAGGUUGGUGCCAACGACGGUGAA ACUAUCGAUAUUGAUUUAAAAGAAAUCAGCUCUAAAACACU GGGACUUGAUAAGCUUAAUGUCCAAGAUGCCUACACCCCGAA AGAAACUGCUGUAACCGUUGAUAAAACUACCUAUAAAAAUG GUACAGAUCCUAUUACAGCCCAGAGCAAUACUGAUAUCCAAA CUGCAAUUGGCGGUGGUGCAACGGGGGUUACUGGGGCUGAU AUCAAAUUUAAAGAUGGUCAAUACUAUUUAGAUGUUAAAGG CGGUGCUUCUGCUGGUGUUUAUAAAGCCACUUAUGAUGAAA CUACAAAGAAAGUUAAUAUUGAUACGACUGAUAAAACUCCG UUGGCAACUGCGGAAGCUACAGCUAUUCGGGGAACGGCCACU AUAACCCACAACCAAAUUGCUGAAGUAACAAAAGAGGGUGU UGAUACGACCACAGUUGCGGCUCAACUUGCUGCAGCAGGGGU UACUGGCGCCGAUAAGGACAAUACUAGCCUUGUAAAACUAUC GUUUGAGGAUAAAAACGGUAAGGUUAUUGAUGGUGGCUAUG CAGUGAAAAUGGGCGACGAUUUCUAUGCCGCUACAUAUGAU GAGAAAACAGGUGCAAUUACUGCUAAAACCACUACUUAUACA GAUGGUACUGGCGUUGCUCAAACUGGAGCUGUGAAAUUUGG UGGCGCAAAUGGUAAAUCUGAAGUUGUUACUGCUACCGAUG GUAAGACUUACUUAGCAAGCGACCUUGACAAACAUAACUUCA GAACAGGCGGUGAGCUUAAAGAGGUUAAUACAGAUAAGACU GAAAACCCACUGCAGAAAAUUGAUGCUGCCUUGGCACAGGUU GAUACACUUCGUUCUGACCUGGGUGCGGUUCAGAACCGUUUC AACUCCGCUAUCACCAACCUGGGCAAUACCGUAAAUAACCUG UCUUCUGCCCGUAGCCGUAUCGAAGAUUCCGACUACGCAACC GAAGUCUCCAACAUGUCUCGCGCGCAGAUUCUGCAGCAGGCC GGUACCUCCGUUCUGGCGCAGGCGAACCAGGUUCCGCAAAAC GUCCUCUCUUUACUGCGU	82
mRNA Sequence (assumes T100 tail)	G*GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUAA GAGCCACCAUGGCACAAGUCAUUAAUACAAACAGCCUGUCGC UGUUGACCCAGAAUAACCUGAACAAAUCCCAGUCCGCACUGG GCACUGCUAUCGAGCGUUUGUCUUCCGGUCUGCGUAUCAACA GCGCGAAAGACGAUGCGGCAGGACAGGCGAUUGCUAACCGUU UUACCGCGAACAUCAAAGGUCUGACUCAGGCUUCCCGUAACG CUAACGACGGUAUCUCCAUUGCGCAGACCACUGAAGGCGCGC UGAACGAAAUCAACAACAACCUGCAGCGUGUGCGUGAACUGG CGGUUCAGUCUGCGAAUGGUACUAACUCCCAGUCUGACCUCG ACUCCAUCCAGGCUGAAAUCACCCAGCGCCUGAACGAAAUCG ACCGUGUAUCCGGCCAGACUCAGUUCAACGGCGUGAAAGUCC UGGCGCAGGACAACACCCUGACCAUCCAGGUUGGUGCCAACG ACGGUGAAACUAUCGAUAUUGAUUUAAAAGAAAUCAGCUCU AAAACACUGGGACUUGAUAAGCUUAAUGUCCAAGAUGCCUAC ACCCCGAAAGAAACUGCUGUAACCGUUGAUAAAACUACCUAU AAAAAUGGUACAGAUCCUAUUACAGCCCAGAGCAAUACUGAU AUCCAAACUGCAAUUGGCGGUGGUGCAACGGGGGUUACUGG GGCUGAUAUCAAAUUUAAAGAUGGUCAAUACUAUUUAGAUG UUAAAGGCGGUGCUUCUGCUGGUGUUUAUAAAGCCACUUAU GAUGAAACUACAAAGAAAGUUAAUAUUGAUACGACUGAUAA AACUCCGUUGGCAACUGCGGAAGCUACAGCUAUUCGGGGAAC GGCCACUAUAACCCACAACCAAAUUGCUGAAGUAACAAAAGA GGGUGUUGAUACGACCACAGUUGCGGCUCAACUUGCUGCAGC AGGGGUUACUGGCGCCGAUAAGGACAAUACUAGCCUUGUAA AACUAUCGUUUGAGGAUAAAAACGGUAAGGUUAUUGAUGGU GGCUAUGCAGUGAAAAUGGGCGACGAUUUCUAUGCCGCUACA UAUGAUGAGAAAACAGGUGCAAUUACUGCUAAAACCACUAC UUAUACAGAUGGUACUGGCGUUGCUCAAACUGGAGCUGUGA AAUUUGGUGGCGCAAAUGGUAAAUCUGAAGUUGUUACUGCU ACCGAUGGUAAGACUUACUUAGCAAGCGACCUUGACAAACAU AACUUCAGAACAGGCGGUGAGCUUAAAGAGGUUAAUACAGA UAAGACUGAAAACCCACUGCAGAAAAUUGAUGCUGCCUUGGC ACAGGUUGAUACACUUCGUUCUGACCUGGGUGCGGUUCAGAA CCGUUUCAACUCCGCUAUCACCAACCUGGGCAAUACCGUAAA	83

TABLE 16-continued

Name	Sequence	SEQ ID NO:
	UAACCUGUCUUCUGCCCGUAGCCGUAUCGAAGAUUCCGACUA CGCAACCGAAGUCUCCAACAUGUCUCGCGCGCAGAUUCUGCA GCAGGCCGGUACCUCCGUUCUGGCGCAGGCGAACCAGGUUCC GCAAAACGUCCUCUCUUUACUGCGUUGAUAAUAGGCUGGAGC CUCGGUGGCCAUGCUUCUUGCCCCUUGGGCCUCCCCCCAGCC CCUCCUCCCCUUCCUGCACCCGUACCCCCGUGGUCUUUGAAU AAAGUCUGAGUGGGCGGCAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAUCUAG	

TABLE 17

Flagellin Amino Acid Sequences

Name	Sequence	SEQ ID NO:
ORF Sequence, AA	MAQVINTNSLSLLTQNNLNKSQSALGTAIERLSSGLRINSAKDDAA GQAIANRFTANIKGLTQASRNANDGISIAQTTEGALNEINNNLQRV RELAVQSANGTNSQSDLDSIQAEITQRLNEIDRVSGQTQFNGVKVL AQDNTLTIQVGANDGETIDIDLKEISSKTLGLDKLNVQDAYTPKET AVTVDKTTYKNGTDPITAQSNTDIQTAIGGGATGVTGADIKFKDG QYYLDVKGGASAGVYKATYDETTKKVNIDTTDKTPLATAEATAI RGTATITHNQIAEVTKEGVDTTTVAAQLAAAGVTGADKDNTSLV KLSFEDKNGKVIDGGYAVKMGDDFYAATYDEKTGAITAKTTTYT DGTGVAQTGAVKFGGANGKSEVVTATDGKTYLASDLDKHNFRT GGELKEVNTDKTENPLQKIDAALAQVDTLRSDLGAVQNRFNSAIT NLGNTVNNLSSARSRIEDSDYATEVSNMSRAQILQQAGTSVLAQA NQVPQNVLSLLR	54
Flagellin-GS linker-circumsporozoite protein (CSP)	MAQVINTNSLSLLTQNNLNKSQSALGTAIERLSSGLRINSAKDDAA GQAIANRFTANIKGLTQASRNANDGISIAQTTEGALNEINNNLQRV RELAVQSANSTNSQSDLDSIQAEITQRLNEIDRVSGQTQFNGVKVL AQDNTLTIQVGANDGETIDIDLKQINSQTLGLDTLNVQQKYKVSD TAATVTGYADTTIALDNSTFKASATGLGGTDQKIDGDLKFDDTTG KYYAKVTVTGGTGKDGYYEVSVDKTNGEVTLAGGATSPLTGGLP ATATEDVKNVQVANADLTEAKAALTAAGVTGTASVVKMSYTDN NGKTIDGGLAVKVGDDYYSATQNKDGSISINTTKYTADDGTSKTA LNKLGGADGKTEVVSIGGKTYAASKAEGHNFKAQPDLAEAAATT TENPLQKIDAALAQVDTLRSDLGAVQNRFNSAITNLGNTVNNLTS ARSRIEDSDYATEVSNMSRAQILQQAGTSVLAQANQVPQNVLSLL RGGGGSGGGGSMMAPDPNANPNANPNANPNANPNANPNANPNA NPNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPN ANPNANPNKNNQGNGQGHNMPNDPNRNVDENANANNAVKNNN NEEPSDKHIEQYLKKIKNSISTEWSPCSVTCGNGIQVRIKPGSANKP KDELDYENDIEKKICKMEKCSSVFNVVNS	55
Flagellin-RPVT linker-circumsporozoite protein (CSP)	MMAPDPNANPNANPNANPNANPNANPNANPNANPNANPN ANPNANPNANPNANPNANPNANPNANPNANPNANPNKNN QGNGQGHNMPNDPNRNVDENANANNAVKNNNNEEPSDKHIEQY LKKIKNSISTEWSPCSVTCGNGIQVRIKPGSANKPKDELDYENDIEK KICKMEKCSSVFNVVNSRPVTMAQVINTNSLSLLTQNNLNKSQSA LGTAIERLSSGLRINSAKDDAAGQAIANRFTANIKGLTQASRNAND GISIAQTTEGALNEINNNLQRVRELAVQSANSTNSQSDLDSIQAEIT QRLNEIDRVSGQTQFNGVKVLAQDNTLTIQVGANDGETIDIDLKQI NSQTLGLDTLNVQQKYKVSDTAATVTGYADTTIALDNSTFKASAT GLGGTDQKIDGDLKFDDTTGKYYAKVTVTGGTGKDGYYEVSVD KTNGEVTLAGGATSPLTGGLPATATEDVKNVQVANADLTEAKAA LTAAGVTGTASVVKMSYTDNNGKTIDGGLAVKVGDDYYSATQN KDGSISINTTKYTADDGTSKTALNKLGGADGKTEVVSIGGKTYAA SKAEGHNFKAQPDLAEAAATTTENPLQKIDAALAQVDTLRSDLG AVQNRFNSAITNLGNTVNNLTSARSRIEDSDYATEVSNMSRAQILQ QAGTSVLAQANQVPQNVLSLLR	56

TABLE 18

Human Metapneumovirus Mutant Amino Acid Sequences

Strain	Sequence	SEQ ID NO:
HMPV_SC_DSCAV1_4MMV	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAICKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LAFAVRELKDFVSKNLTRALNKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGIL CGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWY CQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPC KVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQ DADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFE NIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKK PTGAPPELSGVTNNGFIPHN	85
HMPV_SC_DSTRIC_4MMV	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAICKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGIL CGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWY CQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPC KVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQ DADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEHQWHVALDQVFE NIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKK PTGAPPELSGVTNNGFIPHN	86
HMPV_SC_DM_Krarup_T74LD185P	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLLKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	87
HMPV_SC_TM_Krarup_T74LD185PD454N	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLLKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPENQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	88
HMPV_SC_4M_Krarup_T74LS170LD185P	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLLKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVLKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	89
HMPV_SC_5M_Krarup_T74LS170LD185PD454N	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLLKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVLKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPENQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	90
HMPV_SC_DM_Krarup_E51PT74L	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLPVG DVENLTCSDGPSLIKTELDLLKSALRELKTVSADQLAREEQIENPGSGSFVLG	91

TABLE 18-continued

Human Metapneumovirus Mutant Amino Acid Sequences

Strain	Sequence	SEQ ID NO:
	AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	
HMPV_SC_TM_Krarup_E51PT74LD454N	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLPVG DVENLTCSDGPSLIKTELDLLKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPENQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	92
HMPV_SC_StabilizeAlpha_T74L	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLLKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	93
HMPV_SC_StabilizeAlpha_V55L	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DLENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	94
HMPV_SC_StabilizeAlpha_S170L	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVLKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	95
HMPV_SC_StabilizeAlpha_T174W	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLWRAINKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	96
HMPV_SC_4M_StabilizeAlpha_V55LT74LS170LT174W	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DLENLTCSDGPSLIKTELDLLKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVLKNLWRAINKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS	97

TABLE 18-continued

Human Metapneumovirus Mutant Amino Acid Sequences

Strain	Sequence	SEQ ID NO:
	DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	
HMPV_ProlineStab_E51P	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLPVG DVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	98
HMPV_ProlineStab_D185P	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	99
HMPV_ProlineStab_D183P	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCPIDDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	100
HMPV_ProlineStab_E131P	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLPSEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	101
HMPV_ProlineStab_D447P	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFPPIKFPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	102
HMPV_TrimerRepulsionD454N	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC	103

TABLE 18-continued

Human Metapneumovirus Mutant Amino Acid Sequences

Strain	Sequence	SEQ ID NO:
	QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPENQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	
HMPV_TrimerRepulsionE453N	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPQDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	104
HMPV_StabilizeAlphaF196W	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQWNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	105

TABLE 19

Strain	Nucleic Acid Sequence	SEQ ID NO:
Human Metapneumovirus Mutant Nucleic Acid Sequences		
HMPV_SC_DSCAV1_4MMV	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG CAGGCGTGGCCATCTGCAAGACCATCAGACTGGAAAGCG AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC CTTTGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC CTGACACGGGCCCTGAACAAGAACAAGTGCGACATCGAC GACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGC GGTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGG AATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCT GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG GCCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCG ACGGAAAGGCTTCGGCATTCTGTGTGGCGTGTACGGCAGC AGCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGA TCGACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTG TAGCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGA GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGAC CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG AGCAGAGCAAAGAGTGCAACATCAACATCAGCACCACCA ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC TATGGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTT ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG GCATCATCAAGCAGCTGAACAAGGGCTGCAGCTACATCAC CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC AAGGGCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGT	106

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
	TCCCTGAGGATCAGTTCAACGTGGCCCTGGACCAGGTGTT	
	CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC	
	AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC	
	TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC	
	CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC	
	AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG	
	ACCAACAATGGCTTCATCCCTCACAAC	
HMPV_SC_DSTRIC_4MMV	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	107
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG	
	AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA	
	ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA	
	GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG	
	CAGGCGTGGCCATCTGCAAGACCATCAGACTGGAAAGCG	
	AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG	
	AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC	
	CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC	
	CTGACACGGGCCATTAACAAGAACAAGTGCGACATCGAC	
	GACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGC	
	GGTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGG	
	AATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCT	
	GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG	
	GCCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCG	
	ACGGAAAGGCTTCGGCATTCTGTGTGGCGTGTACGGCAGC	
	AGCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGA	
	TCGACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTG	
	TAGCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGA	
	GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG	
	TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGAC	
	CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG	
	AGCAGAGCAAAGAGTGCAACATCAACATCAGCACCACCA	
	ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC	
	TATGGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTT	
	ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG	
	GCATCATCAAGCAGCTGAACAAGGGCTGCAGCTACATCAC	
	CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG	
	TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC	
	AAGGGCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGT	
	TCCCTGAGCACCAGTGGCATGTGGCCCTGGACCAGGTGTT	
	CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC	
	AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC	
	TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC	
	CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC	
	AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG	
	ACCAACAATGGCTTCATCCCTCACAAC	
HMPV_SC_DM_Krarup_T74LD185P	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	108
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA	
	ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA	
	CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGAG	
	CCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAGC	
	AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCGA	
	AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA	
	GGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGCC	
	ACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAACC	
	TGACACGGGCCATTAACAAGAACAAGTGCGACATCCCTGA	
	CCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCGG	
	TTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGAA	
	TCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTGA	
	GCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGGC	
	CAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGAC	
	GGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCAG	
	CGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATCG	
	ACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTAG	
	CGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGGA	
	CCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTAC	
	TACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCAC	
	GTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAGC	
	AGAGCAAAGAGTGCAACATCAACATCAGCACCACCAACT	

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
	ATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT	
	GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA	
	AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT	
	CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC	
	CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC	
	AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG	
	GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC	
	TGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG	
	AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA	
	GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT	
	CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG	
	ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA	
	AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA	
	CAATGGCTTCATCCCTCACAAC	
HMPV_SC_TM_Krarup_T74LD185PD454N	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	109
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA	
	ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA	
	CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGAG	
	CCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAGC	
	AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCGA	
	AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA	
	GGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGCC	
	ACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAACC	
	TGACACGGGCCATTAACAAGAACAAGTGCGACATCCCTGA	
	CCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCGG	
	TTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGAA	
	TCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTGA	
	GCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGGC	
	CAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGAC	
	GGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCAG	
	CGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATCG	
	ACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTAG	
	CGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGGA	
	CCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTAC	
	TACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCAC	
	GTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAGC	
	AGAGCAAAGAGTGCAACATCAACATCAGCACCACCAACT	
	ATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT	
	GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA	
	AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT	
	CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC	
	CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC	
	AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG	
	GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC	
	TGAGAACCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG	
	AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA	
	GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT	
	CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG	
	ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA	
	AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA	
	CAATGGCTTCATCCCTCACAAC	
HMPV_SC_4M_Krarup_T74LS170LD185P	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	110
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA	
	ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA	
	CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGAG	
	CCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAGC	
	AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCGA	
	AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA	
	GGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGCC	
	ACAGCCGTGCGCGAGCTGAAGGACTTCGTGCTTAAGAACC	
	TGACACGGGCCATTAACAAGAACAAGTGCGACATCCCTGA	
	CCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCGG	
	TTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGAA	
	TCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTGA	
	GCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGGC	
	CAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGAC	
	GGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCAG	

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
	CGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATCG	
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	CGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGGA	
	CCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTAC	
	TACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCAC	
	GTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAGC	
	AGAGCAAAGAGTGCAACATCAACATCAGCACCACCAACT	
	ATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT	
	GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA	
	AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT	
	CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC	
	CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC	
	AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG	
	GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC	
	TGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG	
	AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA	
	GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT	
	CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG	
	ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA	
	AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA	
	CAATGGCTTCATCCCTCACAAC	
HMPV_SC_5M_Krarup_T74LS170LD185PD454N	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	111
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA	
	ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA	
	CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGAG	
	CCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAGC	
	AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCGA	
	AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA	
	GGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGCC	
	ACAGCCGTGCGCGAGCTGAAGGACTTCGTGCTTAAGAACC	
	TGACACGGGCCATTAACAAGAACAAGTGCGACATCCCTGA	
	CCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCGG	
	TTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGAA	
	TCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTGA	
	GCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGGC	
	CAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGAC	
	GGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCAG	
	CGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATCG	
	ACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTAG	
	CGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGGA	
	CCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTAC	
	TACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCAC	
	GTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAGC	
	AGAGCAAAGAGTGCAACATCAACATCAGCACCACCAACT	
	ATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT	
	GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA	
	AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT	
	CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC	
	CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC	
	AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG	
	GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC	
	TGAGAACCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG	
	AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA	
	GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT	
	CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG	
	ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA	
	AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA	
	CAATGGCTTCATCCCTCACAAC	
HMPV_SC_DM_Krarup_E51PT74L	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	112
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGCCTGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA	
	ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA	
	CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGAG	
	CCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAGC	
	AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCGA	
	AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA	
	GGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGCC	
	ACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAACC	

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	GTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGA	
	ATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTG	
	AGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGG	
	CCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGA	
	CGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCA	
	GCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATC	
	GACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTA	
	GCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGG	
	ACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTA	
	CTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCA	
	CGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAG	
	CAGAGCAAAGAGTGCAACATCAACATCAGCACCACCAAC	
	TATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT	
	GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA	
	AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT	
	CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC	
	CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC	
	AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG	
	GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC	
	TGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG	
	AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA	
	GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT	
	CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG	
	ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA	
	AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA	
	CAATGGCTTCATCCCTCACAAC	
HMPV_SC_TM_Krarup_E51PT74LD454N	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	113
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGCCTGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA	
	ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA	
	CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGAG	
	CCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAGC	
	AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCGA	
	AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA	
	GGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGCC	
	ACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAACC	
	TGACACGGGCCATTAACAAGAACAAGTGCGACATCGACG	
	ACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCG	
	GTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGA	
	ATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTG	
	AGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGG	
	CCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGA	
	CGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCA	
	GCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATC	
	GACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTA	
	GCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGG	
	ACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTA	
	CTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCA	
	CGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAG	
	CAGAGCAAAGAGTGCAACATCAACATCAGCACCACCAAC	
	TATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT	
	GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA	
	AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT	
	CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC	
	CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC	
	AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG	
	GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC	
	TGAGAACCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG	
	AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA	
	GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT	
	CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG	
	ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA	
	AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA	
	CAATGGCTTCATCCCTCACAAC	
HMPV_SC_StabilizeAlpha_T74L	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	114
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA	

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	CCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAGC	
	AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCGA	
	AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA	
	GGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGCC	
	ACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAACC	
	TGACACGGGCCATTAACAAGAACAAGTGCGACATCGACG	
	ACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCG	
	GTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGA	
	ATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTG	
	AGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGG	
	CCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGA	
	CGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCA	
	GCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATC	
	GACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTA	
	GCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGG	
	ACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTA	
	CTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCA	
	CGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAG	
	CAGAGCAAAGAGTGCAACATCAACATCAGCACCACCAAC	
	TATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT	
	GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA	
	AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT	
	CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC	
	CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC	
	AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG	
	GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC	
	TGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG	
	AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA	
	GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT	
	CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG	
	ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA	
	AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA	
	CAATGGCTTCATCCCTCACAAC	
HMPV_SC_StabilizeAlpha_V55L	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	115
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACCTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG	
	AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA	
	ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA	
	GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG	
	CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG	
	AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG	
	AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC	
	CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC	
	CTGACACGGGCCATTAACAAGAACAAGTGCGACATCGAC	
	GACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGC	
	GGTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGG	
	AATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCT	
	GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG	
	GCCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCG	
	ACGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGC	
	AGCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGA	
	TCGACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTG	
	TAGCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGA	
	GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG	
	TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGAC	
	CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG	
	AGCAGAGCAAAGAGTGCAACATCAACATCAGCACCACCA	
	ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC	
	TATGGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTT	
	ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG	
	GCATCATCAAGCAGCTGAACAAGGGCTGCAGCTACATCAC	
	CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG	
	TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC	
	AAGGGCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGT	
	TCCCTGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTT	
	CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC	
	AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC	
	TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC	
	CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC	
	AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG	
	ACCAACAATGGCTTCATCCCTCACAAC	

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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HMPV_SC_StabilizeAlpha_T174W	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC CTGTGGCGGGCCATTAACAAGAACAAGTGCGACATCGAC GACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGC GGTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGG AATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCT GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG GCCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCG ACGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGC AGCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGA TCGACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTG TAGCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGA GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGAC CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG AGCAGAGCAAAGAGTGCAACATCAACATCAGCACCACCA ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC TATGGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTT ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG GCATCATCAAGCAGCTGAACAAGGGCTGCAGCTACATCAC CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC AAGGGCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGT	117

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC	
	AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC	
	TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC	
	CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC	
	AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG	
	ACCAACAATGGCTTCATCCCTCACAAC	
HMPV_SC_4M_StabilizeAlpha_V55LT74LS170LT174W	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	118
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACCTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA	
	ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA	
	CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGAG	
	CCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAGC	
	AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCGA	
	AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA	
	GGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGCC	
	ACAGCCGTGCGCGAGCTGAAGGACTTCGTGCTTAAGAACC	
	TGTGGCGGGCCATTAACAAGAACAAGTGCGACATCGACG	
	ACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCG	
	GTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGA	
	ATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTG	
	AGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGG	
	CCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGA	
	CGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCA	
	GCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATC	
	GACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTA	
	GCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGG	
	ACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTA	
	CTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCA	
	CGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAG	
	CAGAGCAAAGAGTGCAACATCAACATCAGCACCACCAAC	
	TATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT	
	GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA	
	AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT	
	CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC	
	CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC	
	AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG	
	GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC	
	TGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG	
	AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA	
	GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT	
	CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG	
	ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA	
	AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA	
	CAATGGCTTCATCCCTCACAAC	
HMPV_ProlineStab_E51P	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	119
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGCCTGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG	
	AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA	
	ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA	
	GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG	
	CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG	
	AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG	
	AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC	
	CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC	
	CTGACACGGGCCATTAACAAGAACAAGTGCGACATCGAC	
	GACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGC	
	GGTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGG	
	AATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCT	
	GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG	
	GCCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCG	
	ACGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGC	
	AGCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGA	
	TCGACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTG	
	TAGCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGA	
	GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG	
	TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGAC	
	CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG	
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TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	GCATCATCAAGCAGCTGAACAAGGGCTGCAGCTACATCAC	
	CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG	
	TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC	
	AAGGGCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGT	
	TCCCTGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTT	
	CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC	
	AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC	
	TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC	
	CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC	
	AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG	
	ACCAACAATGGCTTCATCCCTCACAAC	
HMPV_ProlineStab_D185P	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	120
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG	
	AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA	
	ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA	
	GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG	
	CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG	
	AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG	
	AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC	
	CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC	
	CTGACACGGGCCATTAACAAGAACAAGTGCGACATCCCTG	
	ACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCG	
	GTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGA	
	ATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTG	
	AGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGG	
	CCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGA	
	CGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCA	
	GCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATC	
	GACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTA	
	GCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGG	
	ACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTA	
	CTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCA	
	CGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAG	
	CAGAGCAAAGAGTGCAACATCAACATCAGCACCACCAAC	
	TATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT	
	GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA	
	AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT	
	CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC	
	CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC	
	AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG	
	GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC	
	TGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG	
	AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA	
	GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT	
	CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG	
	ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA	
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	CAATGGCTTCATCCCTCACAAC	
HMPV_ProlineStab_D183P	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	121
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	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG	
	AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA	
	ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA	
	GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG	
	CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG	
	AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG	
	AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC	
	CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC	
	CTGACACGGGCCATTAACAAGAACAAGTGCCCTATCGACG	
	ACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCG	
	GTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGA	
	ATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTG	
	AGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGG	
	CCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGA	
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TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	GCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGG	
	ACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTA	
	CTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCA	
	CGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAG	
	CAGAGCAAAGAGTGCAACATCAACATCAGCACCACCAAC	
	TATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT	
	GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA	
	AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT	
	CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC	
	CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC	
	AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG	
	GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC	
	TGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG	
	AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA	
	GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT	
	CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG	
	ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA	
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	CAATGGCTTCATCCCTCACAAC	
HMPV_ProlineStab_E131P	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	122
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG	
	AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA	
	ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA	
	GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG	
	CAGGCGTGGCCATCGCTAAGACCATCAGACTGCCTAGCGA	
	AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA	
	GGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGCC	
	ACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAACC	
	TGACACGGGCCATTAACAAGAACAAGTGCGACATCGACG	
	ACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCG	
	GTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGA	
	ATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTG	
	AGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGG	
	CCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGA	
	CGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCA	
	GCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATC	
	GACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTA	
	GCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGG	
	ACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTA	
	CTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCA	
	CGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAG	
	CAGAGCAAAGAGTGCAACATCAACATCAGCACCACCAAC	
	TATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT	
	GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA	
	AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT	
	CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC	
	CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC	
	AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG	
	GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC	
	TGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG	
	AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA	
	GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT	
	CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG	
	ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA	
	AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA	
	CAATGGCTTCATCCCTCACAAC	
HMPV_ProlineStab_D447P	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	123
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG	
	AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA	
	ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA	
	GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG	
	CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG	
	AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG	
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TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	AATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCT	
	GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG	
	GCCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCG	
	ACGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGC	
	AGCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGA	
	TCGACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTG	
	TAGCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGA	
	GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG	
	TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGAC	
	CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG	
	AGCAGAGCAAAGAGTGCAACATCAACATCAGCACCACCA	
	ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC	
	TATGGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTT	
	ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG	
	GCATCATCAAGCAGCTGAACAAGGGCTGCAGCTACATCAC	
	CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG	
	TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC	
	AAGGGCAGACCTGTGTCCAGCAGCTTCCCACCTATCAAGT	
	TCCCTGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTT	
	CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC	
	AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC	
	TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC	
	CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC	
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	ACCAACAATGGCTTCATCCCTCACAAC	
HMPV_TrimerRepulsionD454N	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	124
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
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	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG	
	AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA	
	ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA	
	GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG	
	CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG	
	AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG	
	AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC	
	CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC	
	CTGACACGGGCCATTAACAAGAACAAGTGCGACATCGAC	
	GACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGC	
	GGTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGG	
	AATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCT	
	GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG	
	GCCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCG	
	ACGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGC	
	AGCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGA	
	TCGACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTG	
	TAGCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGA	
	GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG	
	TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGAC	
	CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG	
	AGCAGAGCAAAGAGTGCAACATCAACATCAGCACCACCA	
	ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC	
	TATGGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTT	
	ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG	
	GCATCATCAAGCAGCTGAACAAGGGCTGCAGCTACATCAC	
	CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG	
	TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC	
	AAGGGCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGT	
	TCCCTGAGAACCAGTTCCAGGTGGCCCTGGACCAGGTGTT	
	CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC	
	AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC	
	TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC	
	CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC	
	AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG	
	ACCAACAATGGCTTCATCCCTCACAAC	
HMPV_TrimerRepulsionE453N	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	125
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG	

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
	AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA	
	ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA	
	GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG	
	CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG	
	AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG	
	AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC	
	CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC	
	CTGACACGGGCCATTAACAAGAACAAGTGCGACATCGAC	
	GACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGC	
	GGTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGG	
	AATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCT	
	GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG	
	GCCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCG	
	ACGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGC	
	AGCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGA	
	TCGACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTG	
	TAGCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGA	
	GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG	
	TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGAC	
	CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG	
	AGCAGAGCAAAGAGTGCAACATCAACATCAGCACCACCA	
	ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC	
	TATGGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTT	
	ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG	
	GCATCATCAAGCAGCTGAACAAGGGCTGCAGCTACATCAC	
	CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG	
	TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC	
	AAGGGCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGT	
	TCCCTCAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTT	
	CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC	
	AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC	
	TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC	
	CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC	
	AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG	
	ACCAACAATGGCTTCATCCCTCACAAC	
HMPV_StabilizeAlphaF196W	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	126
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG	
	AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA	
	ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA	
	GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG	
	CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG	
	AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG	
	AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC	
	CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC	
	CTGACACGGGCCATTAACAAGAACAAGTGCGACATCGAC	
	GACCTGAAGATGGCCGTGTCCTTTAGCCAGTGGAACCGGC	
	GGTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGG	
	AATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCT	
	GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG	
	GCCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCG	
	ACGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGC	
	AGCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGA	
	TCGACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTG	
	TAGCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGA	
	GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG	
	TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGAC	
	CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG	
	AGCAGAGCAAAGAGTGCAACATCAACATCAGCACCACCA	
	ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC	
	TATGGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTT	
	ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG	
	GCATCATCAAGCAGCTGAACAAGGGCTGCAGCTACATCAC	
	CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG	
	TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC	
	AAGGGCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGT	
	TCCCTGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTT	
	CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC	
	AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC	
	TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC	
	CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC	
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	ACCAACAATGGCTTCATCCCTCACAAC	

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
	Human Metapneumovirus mRNA Sequences	
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HMPV_SC_DSURIC_4MMV	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA GCUGUUACAGCAGGCGUGGCCAUCUGCAAGACCAUCAGA CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU GUGUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	128

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGCACCAGUGGCAUGUGGCCCUGGACCAGGUGUUCGA	
	GAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCAA	
	CAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCUU	
	CAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCUC	
	CAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGAC	
	CAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAGU	
	GACCAACAAUGGCUUCAUCCCUCACAAC	
HMPV_SC_DM_Krarup_U74LD185P	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	129
	CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA	
	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGCUCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG	
	UGCGACAUCCCUGACCUGAAGAUGGCCGUGUCCUUUAGC	
	CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU	
	AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC	
	CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC	
	AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG	
	AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU	
	GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC	
	AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA	
	UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC	
	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG	
	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU	
	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
	CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG	
	UGACCAACAAUGGCUUCAUCCCUCACAAC	
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	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGCUCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG	
	UGCGACAUCCCUGACCUGAAGAUGGCCGUGUCCUUUAGC	
	CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU	
	AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC	
	CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC	
	AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG	
	AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU	
	GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC	
	AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA	
	UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC	

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
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	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGAACCAGUUCCAGGUGGCCCUGGACCAGGUGUUCGA	
	GAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCAA	
	CAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCUU	
	CAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCUC	
	CAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGAC	
	CAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAGU	
	GACCAACAAUGGCUUCAUCCCUCACAAC	
HMPV_SC_4M_Krarup_U74LS170LD185P	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	131
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	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGCUCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGCUUAAGAACCUGACACGGGCCAUUAACAAGAACAA	
	GUGCGACAUCCCUGACCUGAAGAUGGCCGUGUCCUUUAG	
	CCAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUU	
	UAGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGA	
	CCUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAA	
	CAUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGA	
	GAAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUC	
	UGAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUG	
	CAGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGG	
	AUUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGG	
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	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
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	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
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	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
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	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU	
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	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
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	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGCUCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
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TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	CCUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAA	
	CAUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGA	
	GAAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUC	
	UGAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUG	
	CAGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGG	
	AUUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGG	
	CAAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGAACCAGUUCCAGGUGGCCCUGGACCAGGUGUUCGA	
	GAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCAA	
	CAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCUU	
	CAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCUC	
	CAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGAC	
	CAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAGU	
	GACCAACAAUGGCUUCAUCCCUCACAAC	
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	CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA	
	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGCCUGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGCUCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG	
	UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC	
	CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU	
	AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC	
	CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC	
	AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG	
	AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU	
	GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC	
	AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA	
	UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC	
	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG	
	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU	
	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
	CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG	
	UGACCAACAAUGGCUUCAUCCCUCACAAC	
HMPV_SC_UM_Krarup_E51PU74LD454N	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	134
	CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA	
	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGCCUGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG	
	UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC	
	CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU	
	AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC	
	CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC	
	AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG	
	AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU	
	GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC	
	AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA	
	UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC	
	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGAACCAGUUCCAGGUGGCCCUGGACCAGGUGUUCGA	
	GAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCAA	
	CAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCUU	
	CAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCUC	
	CAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGAC	
	CAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAGU	
	GACCAACAAUGGCUUCAUCCCUCACAAC	
HMPV_SC_SUabilizeAlpha_U74L	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	135
	CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA	
	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGCUCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG	
	UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC	
	CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU	
	AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC	
	CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC	
	AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG	
	AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU	
	GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC	
	AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA	
	UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC	
	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG	
	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU	

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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HMPV_SC_SUabilizeAlpha_S170L	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC GUGCUUAAGAACCUGACACGGGCCAUUAACAAGAACAA GUGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAG CCAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUU UAGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGA CCUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAA CAUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGA GAAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUC UGAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUG CAGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGG AUUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGG CAAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	137

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG	
	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU	
	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
	CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG	
	UGACCAACAAUGGCUUCAUCCCUCACAAC	
HMPV_SC_SUabilizeAlpha_U174W	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	138
	CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA	
	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGUCCAAGAACCUGUGGCGGGCCAUUAACAAGAACAA	
	GUGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAG	
	CCAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUU	
	UAGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGA	
	CCUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAA	
	CAUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGA	
	GAAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUC	
	UGAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUG	
	CAGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGG	
	AUUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGG	
	CAAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG	
	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU	
	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
	CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG	
	UGACCAACAAUGGCUUCAUCCCUCACAAC	
HMPV_SC_4M_SUabilizeAlpha_V55LU74LS170LU174W	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	139
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	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACCUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGCUCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGCUUAAGAACCUGUGGCGGGCCAUUAACAAGAACAA	
	GUGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAG	
	CCAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUU	
	UAGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGA	
	CCUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAA	
	CAUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGA	
	GAAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUC	
	UGAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUG	

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	AUUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGG	
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	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG	
	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU	
	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
	CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG	
	UGACCAACAAUGGCUUCAUCCCUCACAAC	
HMPV_ProlineSUab_E51P	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	140
	CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA	
	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGCCUGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG	
	UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC	
	CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU	
	AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC	
	CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC	
	AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG	
	AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU	
	GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC	
	AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA	
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	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
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	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
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	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
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	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG	
	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU	
	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
	CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG	
	UGACCAACAAUGGCUUCAUCCCUCACAAC	
HMPV_ProlineSUab_D185P	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	141
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	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU	
	AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC	
	CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC	
	AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG	
	AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU	
	GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC	
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TABLE 19-continued

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TABLE 19-continued

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TABLE 19-continued

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EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the disclosure described herein. Such equivalents are intended to be encompassed by the following claims.

All references, including patent documents, disclosed herein are incorporated by reference in their entirety.

SEQUENCE LISTING

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<211> LENGTH: 1620
<212> TYPE: DNA
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acaccttgtt ggatcatcaa ggcagctccc tcttgctcag aaaaaaacgg gaattatgct 900

tgcctcctaa gagaggatca agggtggtat tgtaaaaatg caggatctac tgtttactac 960

ccaaatgaaa aagactgcga aacaagaggt gatcatgttt tttgtgacac agcagcaggg 1020

atcaatgttg ctgagcaatc aagagaatgc aacatcaaca tatctactac caactaccca 1080

tgcaaagtca gcacaggaag acaccctata agcatggttg cactatcacc tctcggtgct 1140

ttggtggctt gctataaagg ggtaagctgc tcgattggca gcaattgggt tggaatcatc 1200

aaacaattac ccaaaggctg ctcatacata accaaccagg atgcagacac tgtaacaatt 1260

gacaataccg tgtatcaact aagcaaagtt gaaggtgaac agcatgtaat aaaagggaga 1320

ccagtttcaa gcagttttga tccaatcaag tttcctgagg atcagttcaa tgttgcgctt 1380

gatcaagtct tcgaaagcat tgagaacagt caggcactag tggaccagtc aaacaaaatt 1440

ctaaacagtg cagaaaaagg aaacactggt ttcattatcg tagtaatttt ggttgctgtt 1500

cttggtctaa ccatgatttc agtgagcatc atcatcataa tcaagaaaac aaggaagccc 1560

acaggagcac ctccagagct gaatggtgtc accaacggcg gtttcatacc acatagttag 1620

<210> SEQ ID NO 3
<211> LENGTH: 1620
<212> TYPE: DNA
<213> ORGANISM: Human metapneumovirus

<400> SEQUENCE: 3

atgtcttgga aagtgatgat tatcatttcg ttactcataa cacctcagca tggactaaaa 60

gaaagttatt tagaagaatc atgtagtact ataactgaag gatatctcag tgttttaaga 120

acaggttggt acaccaatgt ctttacatta gaagttggtg atgttgaaaa tcttacatgt 180

actgatggac ctagcttaat caaaacagaa cttgacctaa ccaaaagtgc tttaagagaa 240

ctcaaaacag tttctgctga tcagttagcg agagaagaac aaattgaaaa tcccagacaa 300

tcaaggtttg tcctaggtgc aatagctctt ggagttgcca cagcagcagc agtcacagca 360

ggcattgcaa tagccaaaac tataaggctt gagagtgaag tgaatgcaat caaaggtgct 420

ctcaaaacaa ccaatgaggc agtatcaaca ctaggaaatg gagtgcgggt cctagccact 480

gcagtaagag agctgaaaga atttgtgagc aaaaacctga ctagtgcgat caacaagaac 540

aagtgtgaca ttgctgattt gaagatggct gtcagcttca gtcagttcaa cagaagattc 600

ctaaatgttg tgcggcagtt ttcagacaat gcagggataa caccagcaat atcattggac 660

ctgatgaatg atgctgagct ggccagagct gtatcataca tgccaacatc tgcaggacag 720

ataaaactaa tgttagagaa ccgtgcaatg gtgaggagaa aaggatttgg aatcttgata 780

ggggtctacg gaagctctgt gatttacatg gtccagctgc cgatctttgg tgtcataaat 840

acaccttgtt ggataatcaa ggcagctccc tcttgttcag aaaaagatgg aaattatgct 900

tgcctcctaa gagaggatca agggtggtat tgtaaaaatg caggatccac tgtttactac 960

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ccaaatgaaa aagactgcga aacaagaggt gatcatgttt tttgtgacac agcagcaggg 1020

atcaatgttg ctgagcaatc aagagaatgc aacatcaaca tatctaccac caactaccca 1080

tgcaaagtca gcacaggaag acaccctatc agcatggttg cactatcacc tctcggtgct 1140

ttggtagctt gctacaaagg ggttagctgc tcgactggca gtaatcaggt tggaataatc 1200

aaacaactac ctaaaggctg ctcatacata actaaccagg acgcagacac tgtaacaatt 1260

gacaacactg tgtatcaact aagcaaagtt gagggtgaac agcatgtaat aaaagggaga 1320

ccagtttcaa gcagttttga tccaatcagg tttcctgagg atcagttcaa tgttgcgctt 1380

gatcaagtct ttgaaagcat tgaaaacagt caagcactag tggaccagtc aaacaaaatt 1440

ctgaacagtg cagaaaaagg aaacactggt ttcattattg taataatttt gattgctgtt 1500

cttgggttaa ccatgatttc agtgagcatc atcatcataa tcaaaaaaac aaggaagccc 1560

acaggggcac ctccggagct gaatggtgtt accaacggcg gtttcatacc gcatagttag 1620

<210> SEQ ID NO 4
<211> LENGTH: 1725
<212> TYPE: DNA
<213> ORGANISM: Human respiratory syncytial virus

<400> SEQUENCE: 4

atggagttgc caatcctcaa aacaaatgca attaccacaa tccttgctgc agtcacactc 60

tgtttcgctt ccagtcaaaa catcactgaa gaattttatc aatcaacatg cagtgcagtt 120

agcaaaggct atcttagtgc tctaagaact ggttggtata ctagtgttat aactatagaa 180

ttaagtaata tcaaggaaaa taagtgtaat ggaacagatg ctaaggtaaa attgataaaa 240

caagaattag ataaatataa aaatgctgta acagaattgc agttgctcat gcaaagcaca 300

ccagcagcca acaatcgagc cagaagagaa ctaccaaggt ttatgaatta tacactcaat 360

aataccaaaa ataccaatgt aacattaagc aagaaaagga aaagaagatt tcttggcttt 420

ttgttaggtg ttggatctgc aatcgccagt ggcattgctg tatctaaggt cctgcaccta 480

gaaggggaag tgaacaaaat caaaagtgct ctactatcca caaacaaggc tgtagtcagc 540

ttatcaaatg gagttagtgt cttaaccagc aaagtgttag acctcaaaaa ctatatagat 600

aaacagttgt tacctattgt gaacaagcaa agctgcagca tatcaaacat tgaaactgtg 660

atagagttcc aacaaaagaa caacagacta ctagagatta ccagggaatt tagtgttaat 720

gcaggtgtaa ctacacctgt aagcacttat atgttaacta atagtgaatt attatcatta 780

atcaatgata tgcctataac aaatgatcag aaaaagttaa tgtccaacaa tgttcaaata 840

gttagacagc aaagttactc tatcatgtcc ataataaagg aggaagtctt agcatatgta 900

gtacaattac cactatatgg tgtaatagat acaccctgtt ggaaactgca cacatcccct 960

ctatgtacaa ccaacacaaa ggaagggtcc aacatctgct taacaagaac cgacagagga 1020

tggtattgtg acaatgcagg atcagtatct ttcttcccac aagctgaaac atgtaaagtt 1080

caatcgaatc gggtattttg tgacacaatg aacagtttaa cattaccaag tgaagtaaat 1140

ctctgcaaca ttgacatatt caaccccaaa tatgattgca aaattatgac ttcaaaaaca 1200

gatgtaagca gctccgttat cacatctcta ggagccattg tgtcatgcta tggcaaaact 1260

aaatgtacag catccaataa aaatcgtggg atcataaaga cattttctaa cgggtgtgat 1320

tatgtatcaa ataagggggt ggatactgtg tctgtaggta atacattata ttatgtaaat 1380

aagcaagaag gcaaaagtct ctatgtaaaa ggtgaaccaa taataaattt ctatgaccca 1440

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ttagtgttcc cctctgatga atttgatgca tcaatatctc aagtcaatga gaagattaac 1500

cagagcctag catttattcg taaatccgat gaattattac ataatgtaaa tgctggtaaa 1560

tccaccacaa atatcatgat aactactata attatagtga ttatagtaat attgttatca 1620

ttaattgcag ttggactgct cctatactgc aaggccagaa gcacaccagt cacactaagt 1680

aaggatcaac tgagtggtat aaataatatt gcatttagta actga 1725

<210> SEQ ID NO 5
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Human metapneumovirus isolate

<400> SEQUENCE: 5

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1 5 10 15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
20 25 30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
50 55 60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65 70 75 80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
85 90 95

Asn Pro Arg Gln Ser Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val
100 105 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
115 120 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
130 135 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145 150 155 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
165 170 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
180 185 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
210 215 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225 230 235 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
245 250 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
260 265 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
275 280 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
290 295 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305 310 315 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp

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                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 6
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Human metapneumovirus

<400> SEQUENCE: 6

Met Ser Trp Lys Val Met Ile Ile Ile Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Arg Gln Ser Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Thr Ala Ala Ala Val Thr Ala Gly Ile Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Asn Ala Ile Lys Gly Ala Leu Lys Gln Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160
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Ala Val Arg Glu Leu Lys Glu Phe Val Ser Lys Asn Leu Thr Ser Ala
                165                 170                 175

Ile Asn Arg Asn Lys Cys Asp Ile Ala Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Ser Tyr Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Asn Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Trp Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Ser Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Lys Ile
465                 470                 475                 480

Leu Asn Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Val Ile
                485                 490                 495

Leu Val Ala Val Leu Gly Leu Thr Met Ile Ser Val Ser Ile Ile Ile
            500                 505                 510

Ile Ile Lys Lys Thr Arg Lys Pro Thr Gly Ala Pro Pro Glu Leu Asn
        515                 520                 525

Gly Val Thr Asn Gly Gly Phe Ile Pro His Ser
    530                 535


<210> SEQ ID NO 7
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Human metapneumovirus

<400> SEQUENCE: 7
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Met Ser Trp Lys Val Met Ile Ile Ile Ser Leu Leu Ile Thr Pro Gln
1               5                  10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Arg Gln Ser Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Thr Ala Ala Ala Val Thr Ala Gly Ile Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Asn Ala Ile Lys Gly Ala Leu Lys Thr Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Glu Phe Val Ser Lys Asn Leu Thr Ser Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Ala Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Asn Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Ser Tyr Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asn Thr Pro Cys Trp Ile Ile Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Thr Gly Ser Asn Gln Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415
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Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Arg Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Ser Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Lys Ile
465                 470                 475                 480

Leu Asn Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Leu Thr Met Ile Ser Val Ser Ile Ile Ile
            500                 505                 510

Ile Ile Lys Lys Thr Arg Lys Pro Thr Gly Ala Pro Pro Glu Leu Asn
        515                 520                 525

Gly Val Thr Asn Gly Gly Phe Ile Pro His Ser
    530                 535


<210> SEQ ID NO 8
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Human respiratory syncytial virus

<400> SEQUENCE: 8

Met Glu Leu Pro Ile Leu Lys Thr Asn Ala Ile Thr Thr Ile Leu Ala
1               5                   10                  15

Ala Val Thr Leu Cys Phe Ala Ser Ser Gln Asn Ile Thr Glu Glu Phe
            20                  25                  30

Tyr Gln Ser Thr Cys Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu
        35                  40                  45

Arg Thr Gly Trp Tyr Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile
    50                  55                  60

Lys Glu Asn Lys Cys Asn Gly Thr Asp Ala Lys Val Lys Leu Ile Lys
65                  70                  75                  80

Gln Glu Leu Asp Lys Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu
                85                  90                  95

Met Gln Ser Thr Pro Ala Ala Asn Asn Arg Ala Arg Arg Glu Leu Pro
            100                 105                 110

Arg Phe Met Asn Tyr Thr Leu Asn Asn Thr Lys Asn Thr Asn Val Thr
        115                 120                 125

Leu Ser Lys Lys Arg Lys Arg Arg Phe Leu Gly Phe Leu Leu Gly Val
    130                 135                 140

Gly Ser Ala Ile Ala Ser Gly Ile Ala Val Ser Lys Val Leu His Leu
145                 150                 155                 160

Glu Gly Glu Val Asn Lys Ile Lys Ser Ala Leu Leu Ser Thr Asn Lys
                165                 170                 175

Ala Val Val Ser Leu Ser Asn Gly Val Ser Val Leu Thr Ser Lys Val
            180                 185                 190

Leu Asp Leu Lys Asn Tyr Ile Asp Lys Gln Leu Leu Pro Ile Val Asn
        195                 200                 205

Lys Gln Ser Cys Ser Ile Ser Asn Ile Glu Thr Val Ile Glu Phe Gln
    210                 215                 220

Gln Lys Asn Asn Arg Leu Leu Glu Ile Thr Arg Glu Phe Ser Val Asn
225                 230                 235                 240

Ala Gly Val Thr Thr Pro Val Ser Thr Tyr Met Leu Thr Asn Ser Glu
                245                 250                 255
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Leu Leu Ser Leu Ile Asn Asp Met Pro Ile Thr Asn Asp Gln Lys Lys
            260                 265                 270

Leu Met Ser Asn Asn Val Gln Ile Val Arg Gln Gln Ser Tyr Ser Ile
        275                 280                 285

Met Ser Ile Ile Lys Glu Glu Val Leu Ala Tyr Val Val Gln Leu Pro
    290                 295                 300

Leu Tyr Gly Val Ile Asp Thr Pro Cys Trp Lys Leu His Thr Ser Pro
305                 310                 315                 320

Leu Cys Thr Thr Asn Thr Lys Glu Gly Ser Asn Ile Cys Leu Thr Arg
                325                 330                 335

Thr Asp Arg Gly Trp Tyr Cys Asp Asn Ala Gly Ser Val Ser Phe Phe
            340                 345                 350

Pro Gln Ala Glu Thr Cys Lys Val Gln Ser Asn Arg Val Phe Cys Asp
        355                 360                 365

Thr Met Asn Ser Leu Thr Leu Pro Ser Glu Val Asn Leu Cys Asn Ile
    370                 375                 380

Asp Ile Phe Asn Pro Lys Tyr Asp Cys Lys Ile Met Thr Ser Lys Thr
385                 390                 395                 400

Asp Val Ser Ser Ser Val Ile Thr Ser Leu Gly Ala Ile Val Ser Cys
                405                 410                 415

Tyr Gly Lys Thr Lys Cys Thr Ala Ser Asn Lys Asn Arg Gly Ile Ile
            420                 425                 430

Lys Thr Phe Ser Asn Gly Cys Asp Tyr Val Ser Asn Lys Gly Val Asp
        435                 440                 445

Thr Val Ser Val Gly Asn Thr Leu Tyr Tyr Val Asn Lys Gln Glu Gly
    450                 455                 460

Lys Ser Leu Tyr Val Lys Gly Glu Pro Ile Ile Asn Phe Tyr Asp Pro
465                 470                 475                 480

Leu Val Phe Pro Ser Asp Glu Phe Asp Ala Ser Ile Ser Gln Val Asn
                485                 490                 495

Glu Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg Lys Ser Asp Glu Leu
            500                 505                 510

Leu His Asn Val Asn Ala Gly Lys Ser Thr Thr Asn Ile Met Ile Thr
        515                 520                 525

Thr Ile Ile Ile Val Ile Ile Val Ile Leu Leu Ser Leu Ile Ala Val
    530                 535                 540

Gly Leu Leu Leu Tyr Cys Lys Ala Arg Ser Thr Pro Val Thr Leu Ser
545                 550                 555                 560

Lys Asp Gln Leu Ser Gly Ile Asn Asn Ile Ala Phe Ser Asn
                565                 570


<210> SEQ ID NO 9
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Human parainfluenza virus 3

<400> SEQUENCE: 9

atgccaattt caatactgtt aattattaca accatgatca tggcatcaca ctgccaaata     60

gacatcacaa aactacagca tgtaggtgta ttggtcaaca gtcccaaagg gatgaagata    120

tcacaaaact tcgaaacaag atatctaatc ctgagtctca taccaaaaat agaagattct    180

aactcttgtg gtgaccaaca gatcaagcaa tacaagaggt tattggatag actgatcatt    240

cctttatatg atggactaag attacagaag gatgtgatag tgactaatca agaatccaat    300
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gaaaacactg atcccagaac agaacgattc tttggagggg taattggaac tattgctcta 360

ggagtagcaa cctcagcaca aattacagca gcagttgctc tggttgaagc caagcaggca 420

agatcagaca ttgaaaaact caaggaagca atcagggaca caaataaagc agtgcagtca 480

gttcagagct ctgtaggaaa tttgatagta gcaattaaat cagtccagga ttatgtcaac 540

aaagaaatcg tgccatcgat tgcgagacta ggttgtgaag cagcaggact tcagttaggg 600

attgcattaa cacagcatta ctcagaatta acaaatatat ttggtgataa cataggatcg 660

ttacaagaaa aaggaataaa attacaaggt atagcatcat tataccgtac aaatatcaca 720

gaaatattca caacatcaac agttgacaaa tatgatattt atgatctatt atttacagaa 780

tcaataaagg tgagagttat agatgttgat ttgaatgatt actcaataac cctccaagtc 840

agactccctt tattgaccag actgctgaac actcaaatct acaaagtaga ttccatatca 900

tacaatatcc aaaatagaga atggtatatc cctcttccca gccatatcat gacgaaaggg 960

gcatttctag gtggagcaga tgtcaaagaa tgcatagaag cattcagcag ttatatatgc 1020

ccttctgatc caggatttgt actaaaccat gaaatggaga gctgtctatc aggaaacata 1080

tcccaatgtc caagaaccac agtcacatca gacatagttc ctaggtatgc atttgtcaat 1140

ggaggagtgg ttgcgaattg tataacaact acatgtacat gcaatggtat cggtaataga 1200

atcaaccaac cacctgatca aggagtcaaa attataacac ataaagaatg taatacaata 1260

ggtatcaacg gaatgctatt caacacaaac aaagaaggaa ctcttgcatt ctacacacca 1320

gacgacataa cattaaacaa ttctgttgca cttgatccga ttgacatatc aatcgagctc 1380

aacaaggcca aatcagatct tgaggaatca aaagaatgga taagaaggtc aaatcaaaag 1440

ctagattcta ttggaagttg gcatcaatct agcactacaa tcatagttat tttgataatg 1500

atgattatat tgtttataat taatataaca ataattacaa ttgcaattaa gtattacaga 1560

attcaaaaga gaaatcgagt ggatcaaaat gataagccgt atgtattaac aaacaag 1617

<210> SEQ ID NO 10
<211> LENGTH: 1716
<212> TYPE: DNA
<213> ORGANISM: Human parainfluenza virus 3

<400> SEQUENCE: 10

atggaatact ggaagcacac caaccacgga aaggatgctg gtaatgagct ggagacatcc 60

acagccactc atggcaacaa gctcaccaac aagataacat atatattgtg gacgataacc 120

ctggtgttat tatcaatagt cttcatcata gtgctaacta attccatcaa aagtgaaaag 180

gcccgcgaat cattgctaca agacataaat aatgagttta tggaagttac agaaaagatc 240

caagtggcat cggataatac taatgatcta atacagtcag gagtgaatac aaggcttctt 300

acaattcaga gtcatgtcca gaattatata ccaatatcat tgacacaaca aatatcggat 360

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agaataacac atgatgtggg tataaaacct ttaaatccag atgatttctg gagatgcacg 480

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tatcaagtat tacagatagg gataataact gtaaactcag acttggtacc tgacttaaat 720

cctaggatct ctcatacctt caacataaat gacaatagaa agtcatgttc tctagcactc 780

ctaaatacag atgtatatca actgtgttca accccaaaag ttgatgaaag atcagattat 840

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acaacaagat ttaagaataa taatataagt tttgatcaac catatgcggc attataccca 960

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gaacatccaa taaatgagaa tgcaatctgc aacacaactg ggtgtcctgg gaaaacacag 1080

agagactgta atcaagcatc tcatagtcca tggttttcag atagaaggat ggtcaactct 1140

ataattgttg ttgacaaggg cttgaactca gttccaaaat tgaaggtatg gacgatatct 1200

atgagacaaa attactgggg gtcagaagga agattacttc tactaggtaa caagatctac 1260

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gactacagtg atataaggat aaaatggaca tggcataatg tgctatcaag accaggaaac 1380

aatgaatgtc catggggaca ttcatgtccg gatggatgta taacgggagt atataccgat 1440

gcatatccac tcaatcccac aggaagcatt gtatcatctg tcatattgga ctcacaaaaa 1500

tcgagagtca acccagtcat aacttactca acagcaaccg aaagggtaaa cgagctggct 1560

atccgaaaca aaacactctc agctgggtac acaacaacaa gctgcattac acactataac 1620

aaagggtatt gttttcatat agtagaaata aatcataaaa gcttaaacac atttcaaccc 1680

atgttgttca aaacagagat tccaaaaagc tgcagt 1716

<210> SEQ ID NO 11
<211> LENGTH: 1716
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 11

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ctggtgctgc tgagcatcgt gttcatcatc gtgctgacca atagcatcaa gagcgagaag 180

gccagagaga gcctgctgca ggacatcaac aacgagttca tggaagtgac cgagaagatc 240

caggtggcca gcgacaacac caacgacctg atccagagcg gcgtgaacac ccggctgctg 300

accatccaga gccacgtgca gaactacatc cccatcagcc tgacccagca gatcagcgac 360

ctgcggaagt tcatcagcga gatcaccatc cggaacgaca accaggaagt gccccccag 420

agaatcaccc acgacgtggg catcaagccc ctgaaccccg acgatttctg gcggtgtaca 480

agcggcctgc ccagcctgat gaagaccccc aagatccggc tgatgcctgg ccctggactg 540

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<210> SEQ ID NO 12
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 12

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gtgcagtcca gcgtgggcaa tctgatcgtg gccatcaagt ccgtgcagga ctacgtgaac 540

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<210> SEQ ID NO 13
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Human parainfluenza virus 3

<400> SEQUENCE: 13

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His Cys Gln Ile Asp Ile Thr Lys Leu Gln His Val Gly Val Leu Val
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Asn Ser Pro Lys Gly Met Lys Ile Ser Gln Asn Phe Glu Thr Arg Tyr
35 40 45

Leu Ile Leu Ser Leu Ile Pro Lys Ile Glu Asp Ser Asn Ser Cys Gly
50 55 60

Asp Gln Gln Ile Lys Gln Tyr Lys Arg Leu Leu Asp Arg Leu Ile Ile
65 70 75 80

Pro Leu Tyr Asp Gly Leu Arg Leu Gln Lys Asp Val Ile Val Thr Asn
85 90 95

Gln Glu Ser Asn Glu Asn Thr Asp Pro Arg Thr Glu Arg Phe Phe Gly
100 105 110

Gly Val Ile Gly Thr Ile Ala Leu Gly Val Ala Thr Ser Ala Gln Ile
115 120 125

Thr Ala Ala Val Ala Leu Val Glu Ala Lys Gln Ala Arg Ser Asp Ile
130 135 140

Glu Lys Leu Lys Glu Ala Ile Arg Asp Thr Asn Lys Ala Val Gln Ser
145 150 155 160

Val Gln Ser Ser Val Gly Asn Leu Ile Val Ala Ile Lys Ser Val Gln
165 170 175

Asp Tyr Val Asn Lys Glu Ile Val Pro Ser Ile Ala Arg Leu Gly Cys
180 185 190

Glu Ala Ala Gly Leu Gln Leu Gly Ile Ala Leu Thr Gln His Tyr Ser
195 200 205

Glu Leu Thr Asn Ile Phe Gly Asp Asn Ile Gly Ser Leu Gln Glu Lys
210 215 220

Gly Ile Lys Leu Gln Gly Ile Ala Ser Leu Tyr Arg Thr Asn Ile Thr
225 230 235 240

Glu Ile Phe Thr Thr Ser Thr Val Asp Lys Tyr Asp Ile Tyr Asp Leu
245 250 255

Leu Phe Thr Glu Ser Ile Lys Val Arg Val Ile Asp Val Asp Leu Asn
260 265 270

Asp Tyr Ser Ile Thr Leu Gln Val Arg Leu Pro Leu Leu Thr Arg Leu
275 280 285

Leu Asn Thr Gln Ile Tyr Lys Val Asp Ser Ile Ser Tyr Asn Ile Gln
290 295 300

Asn Arg Glu Trp Tyr Ile Pro Leu Pro Ser His Ile Met Thr Lys Gly
305 310 315 320

Ala Phe Leu Gly Gly Ala Asp Val Lys Glu Cys Ile Glu Ala Phe Ser
325 330 335

Ser Tyr Ile Cys Pro Ser Asp Pro Gly Phe Val Leu Asn His Glu Met
340 345 350

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Glu Ser Cys Leu Ser Gly Asn Ile Ser Gln Cys Pro Arg Thr Thr Val
        355                 360                 365

Thr Ser Asp Ile Val Pro Arg Tyr Ala Phe Val Asn Gly Gly Val Val
    370                 375                 380

Ala Asn Cys Ile Thr Thr Thr Cys Thr Cys Asn Gly Ile Gly Asn Arg
385                 390                 395                 400

Ile Asn Gln Pro Pro Asp Gln Gly Val Lys Ile Ile Thr His Lys Glu
                405                 410                 415

Cys Asn Thr Ile Gly Ile Asn Gly Met Leu Phe Asn Thr Asn Lys Glu
            420                 425                 430

Gly Thr Leu Ala Phe Tyr Thr Pro Asp Asp Ile Thr Leu Asn Asn Ser
        435                 440                 445

Val Ala Leu Asp Pro Ile Asp Ile Ser Ile Glu Leu Asn Lys Ala Lys
    450                 455                 460

Ser Asp Leu Glu Glu Ser Lys Glu Trp Ile Arg Arg Ser Asn Gln Lys
465                 470                 475                 480

Leu Asp Ser Ile Gly Ser Trp His Gln Ser Ser Thr Thr Ile Ile Val
                485                 490                 495

Ile Leu Ile Met Met Ile Ile Leu Phe Ile Ile Asn Ile Thr Ile Ile
            500                 505                 510

Thr Ile Ala Ile Lys Tyr Tyr Arg Ile Gln Lys Arg Asn Arg Val Asp
        515                 520                 525

Gln Asn Asp Lys Pro Tyr Val Leu Thr Asn Lys
    530                 535


<210> SEQ ID NO 14
<211> LENGTH: 572
<212> TYPE: PRT
<213> ORGANISM: Human parainfluenza virus 3

<400> SEQUENCE: 14

Met Glu Tyr Trp Lys His Thr Asn His Gly Lys Asp Ala Gly Asn Glu
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Leu Glu Thr Ser Thr Ala Thr His Gly Asn Lys Leu Thr Asn Lys Ile
            20                  25                  30

Thr Tyr Ile Leu Trp Thr Ile Thr Leu Val Leu Leu Ser Ile Val Phe
        35                  40                  45

Ile Ile Val Leu Thr Asn Ser Ile Lys Ser Glu Lys Ala Arg Glu Ser
    50                  55                  60

Leu Leu Gln Asp Ile Asn Asn Glu Phe Met Glu Val Thr Glu Lys Ile
65                  70                  75                  80

Gln Val Ala Ser Asp Asn Thr Asn Asp Leu Ile Gln Ser Gly Val Asn
                85                  90                  95

Thr Arg Leu Leu Thr Ile Gln Ser His Val Gln Asn Tyr Ile Pro Ile
            100                 105                 110

Ser Leu Thr Gln Gln Ile Ser Asp Leu Arg Lys Phe Ile Ser Glu Ile
        115                 120                 125

Thr Ile Arg Asn Asp Asn Gln Glu Val Pro Pro Gln Arg Ile Thr His
    130                 135                 140

Asp Val Gly Ile Lys Pro Leu Asn Pro Asp Asp Phe Trp Arg Cys Thr
145                 150                 155                 160

Ser Gly Leu Pro Ser Leu Met Lys Thr Pro Lys Ile Arg Leu Met Pro
                165                 170                 175

Gly Pro Gly Leu Leu Ala Met Pro Thr Thr Val Asp Gly Cys Val Arg
            180                 185                 190
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Thr Pro Ser Leu Val Ile Asn Asp Leu Ile Tyr Ala Tyr Thr Ser Asn
        195                 200                 205

Leu Ile Thr Arg Gly Cys Gln Asp Ile Gly Lys Ser Tyr Gln Val Leu
    210                 215                 220

Gln Ile Gly Ile Ile Thr Val Asn Ser Asp Leu Val Pro Asp Leu Asn
225                 230                 235                 240

Pro Arg Ile Ser His Thr Phe Asn Ile Asn Asp Asn Arg Lys Ser Cys
                245                 250                 255

Ser Leu Ala Leu Leu Asn Thr Asp Val Tyr Gln Leu Cys Ser Thr Pro
            260                 265                 270

Lys Val Asp Glu Arg Ser Asp Tyr Ala Ser Ser Gly Ile Glu Asp Ile
        275                 280                 285

Val Leu Asp Ile Val Asn Tyr Asp Gly Ser Ile Ser Thr Thr Arg Phe
    290                 295                 300

Lys Asn Asn Asn Ile Ser Phe Asp Gln Pro Tyr Ala Ala Leu Tyr Pro
305                 310                 315                 320

Ser Val Gly Pro Gly Ile Tyr Tyr Lys Gly Lys Ile Ile Phe Leu Gly
                325                 330                 335

Tyr Gly Gly Leu Glu His Pro Ile Asn Glu Asn Ala Ile Cys Asn Thr
            340                 345                 350

Thr Gly Cys Pro Gly Lys Thr Gln Arg Asp Cys Asn Gln Ala Ser His
        355                 360                 365

Ser Pro Trp Phe Ser Asp Arg Arg Met Val Asn Ser Ile Ile Val Val
    370                 375                 380

Asp Lys Gly Leu Asn Ser Val Pro Lys Leu Lys Val Trp Thr Ile Ser
385                 390                 395                 400

Met Arg Gln Asn Tyr Trp Gly Ser Glu Gly Arg Leu Leu Leu Leu Gly
                405                 410                 415

Asn Lys Ile Tyr Ile Tyr Thr Arg Ser Thr Ser Trp His Ser Lys Leu
            420                 425                 430

Gln Leu Gly Ile Ile Asp Ile Thr Asp Tyr Ser Asp Ile Arg Ile Lys
        435                 440                 445

Trp Thr Trp His Asn Val Leu Ser Arg Pro Gly Asn Asn Glu Cys Pro
    450                 455                 460

Trp Gly His Ser Cys Pro Asp Gly Cys Ile Thr Gly Val Tyr Thr Asp
465                 470                 475                 480

Ala Tyr Pro Leu Asn Pro Thr Gly Ser Ile Val Ser Ser Val Ile Leu
                485                 490                 495

Asp Ser Gln Lys Ser Arg Val Asn Pro Val Ile Thr Tyr Ser Thr Ala
            500                 505                 510

Thr Glu Arg Val Asn Glu Leu Ala Ile Arg Asn Lys Thr Leu Ser Ala
        515                 520                 525

Gly Tyr Thr Thr Thr Ser Cys Ile Thr His Tyr Asn Lys Gly Tyr Cys
    530                 535                 540

Phe His Ile Val Glu Ile Asn His Lys Ser Leu Asn Thr Phe Gln Pro
545                 550                 555                 560

Met Leu Phe Lys Thr Glu Ile Pro Lys Ser Cys Ser
                565                 570


<210> SEQ ID NO 15
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 15

Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15

Asp Thr Thr Gly
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<210> SEQ ID NO 16
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 16

Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser

<210> SEQ ID NO 17
<211> LENGTH: 24
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 17

Met Leu Gly Ser Asn Ser Gly Gln Arg Val Val Phe Thr Ile Leu Leu
1 5 10 15

Leu Leu Val Ala Pro Ala Tyr Ser
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<210> SEQ ID NO 18
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 18

Met Lys Cys Leu Leu Tyr Leu Ala Phe Leu Phe Ile Gly Val Asn Cys
1 5 10 15

Ala

<210> SEQ ID NO 19
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 19

Met Trp Leu Val Ser Leu Ala Ile Val Thr Ala Cys Ala Gly Ala
1 5 10 15

<210> SEQ ID NO 20
<211> LENGTH: 4062
<212> TYPE: DNA
<213> ORGANISM: Middle East respiratory syndrome coronavirus

<400> SEQUENCE: 20

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ggccgtacat attctaacat aactatcact tatcaaggtc tttttcccta tcagggagac 240

catggtgata tgtatgttta ctctgcagga catgctacag gcacaactcc acaaaagttg 300

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atagacctta aagagcttgg caattatact tattacaaca aatggccgtg gtacatttgg 3900

cttggtttca ttgctgggct tgttgcctta gctctatgcg tcttcttcat actgtgctgc 3960

actggttgtg gcacaaactg tatgggaaaa cttaagtgta atcgttgttg tgatagatac 4020

gaggaatacg acctcgagcc gcataaggtt catgttcact aa 4062

<210> SEQ ID NO 21
<211> LENGTH: 4062
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 21

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gataaaactt ggcctaggcc aattgatgtt tctaaggctg acggtattat ataccctcaa 180

ggccgtacat attctaacat aactatcact tatcaaggtc tttttcccta tcagggagac 240

catggtgata tgtatgttta ctctgcagga catgctacag gcacaactcc acaaaagttg 300

tttgtagcta actattctca ggacgtcaaa cagtttgcta atgggtttgt cgtccgtata 360

ggagcagctg ccaattccac tggcactgtt attattagcc catctaccag cgctactata 420

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agagcttttt attgtattct ggagcctcgc tctggaaatc attgtcctgc tggcaattcc 600

tatacttctt ttgccactta tcacactcct gcaacagatt gttctgatgg caattacaat 660

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cgttctatcc aaagtgatag aaaagcttgg gctgccttct acgtatataa acttcaaccg 960

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cgtttggttt ttaccaattg caattataat cttaccaaat tgctttcact tttttctgtg 1260

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tataggaaac aactatctcc acttgaaggt ggtggctggc ttgttgctag tggctcaact 1680

gttgccatga ctgagcaatt acagatgggc tttggtatta cagttcaata tggtacagac 1740

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tccattgctt ttaatcatcc tattcaggtt gatcaactta atagtagtta ttttaaatta 2340

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gttgatgagt ggtcatatac tggctcgtcc ttctatgcac ctgagcccat tacctccctt 3600

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aatgttagca ccagtatacc taattttggt tccctaacac agattaatac tacattactc 3780

gatcttacct acgagatgtt gtctcttcaa caagttgtta aagcccttaa tgagtcttac 3840

atagacctta aagagcttgg caattatact tattacaaca aatggccgtg gtacatttgg 3900

cttggtttca ttgctgggct tgttgcctta gctctatgcg tcttcttcat actgtgctgc 3960

actggttgtg gcacaaactg tatgggaaaa cttaagtgta atcgttgttg tgatagatac 4020

gaggaatacg acctcgagcc gcataaggtt catgttcact aa 4062

<210> SEQ ID NO 22
<211> LENGTH: 1845
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 22

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tccgtgcggt cggtgcctgg cgaaatgcgg ctggcctcca tcgccttcaa tcacccaatc 180

caagtggatc agctgaatag ctcgtatttc aagctgtcca tccccacgaa cttctcgttc 240

ggggtcaccc aggagtacat ccagaccaca attcagaagg tcaccgtcga ttgcaagcaa 300

tacgtgtgca acggcttcca gaagtgcgag cagctgctga gagaatacgg gcagttttgc 360

agcaagatca accaggcgct gcatggagct aacttgcgcc aggacgactc cgtgcgcaac 420

ctctttgcct ctgtgaagtc atcccagtcc tccccaatca tcccgggatt cggaggggac 480

ttcaacctga ccctcctgga gcccgtgtcg atcagcaccg gtagcagatc ggcgcgctca 540

gccattgaag atcttctgtt cgacaaggtc accatcgccg atccgggcta catgcaggga 600

tacgacgact gtatgcagca gggaccagcc tccgcgaggg acctcatctg cgcgcaatac 660

gtggccgggt acaaagtgct gcctcctctg atggatgtga acatggaggc cgcttatact 720

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cagactggat tcactacgac taacgaagcg ttccagaagg tccaggacgc tgtgaacaac 960

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gcatcgatcg gtgacataat tcagcggctg gacgtgctgg agcaggacgc ccagatcgac 1080

cgcctcatca acggacggct gaccaccttg aatgccttcg tggcacaaca gctggtccgg 1140

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ttcggaagcc tgacacagat caacaccacc cttctcgacc tgacctacga gatgctgagc 1680

cttcaacaag tggtcaaggc cctgaacgag agctacatcg acctgaagga gctgggcaac 1740

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<210> SEQ ID NO 23
<211> LENGTH: 4071
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 23

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cagacctttt tcgacaagac ctggcccaga cccatcgacg tgtccaaggc cgacggcatc 180

atctatccac aaggccggac ctacagcaac atcaccatta cctaccaggg cctgttccca 240

tatcaaggcg accacggcga tatgtacgtg tactctgccg gccacgccac cggcaccaca 300

ccccagaaac tgttcgtggc caactacagc caggacgtga agcagttcgc caacggcttc 360

gtcgtgcgga ttggcgccgc tgccaatagc accggcacag tgatcatcag ccccagcacc 420

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<210> SEQ ID NO 24
<211> LENGTH: 1353
<212> TYPE: PRT
<213> ORGANISM: Middle East respiratory syndrome coronavirus

<400> SEQUENCE: 24

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Ser Tyr Val Asp Val Gly Pro Asp Ser Val Lys Ser Ala Cys Ile Glu
            20                  25                  30

Val Asp Ile Gln Gln Thr Phe Phe Asp Lys Thr Trp Pro Arg Pro Ile
        35                  40                  45

Asp Val Ser Lys Ala Asp Gly Ile Ile Tyr Pro Gln Gly Arg Thr Tyr
    50                  55                  60

Ser Asn Ile Thr Ile Thr Tyr Gln Gly Leu Phe Pro Tyr Gln Gly Asp
65                  70                  75                  80

His Gly Asp Met Tyr Val Tyr Ser Ala Gly His Ala Thr Gly Thr Thr
                85                  90                  95

Pro Gln Lys Leu Phe Val Ala Asn Tyr Ser Gln Asp Val Lys Gln Phe
            100                 105                 110

Ala Asn Gly Phe Val Val Arg Ile Gly Ala Ala Ala Asn Ser Thr Gly
        115                 120                 125

Thr Val Ile Ile Ser Pro Ser Thr Ser Ala Thr Ile Arg Lys Ile Tyr
    130                 135                 140

Pro Ala Phe Met Leu Gly Ser Ser Val Gly Asn Phe Ser Asp Gly Lys
145                 150                 155                 160

Met Gly Arg Phe Phe Asn His Thr Leu Val Leu Leu Pro Asp Gly Cys
                165                 170                 175

Gly Thr Leu Leu Arg Ala Phe Tyr Cys Ile Leu Glu Pro Arg Ser Gly
            180                 185                 190

Asn His Cys Pro Ala Gly Asn Ser Tyr Thr Ser Phe Ala Thr Tyr His
        195                 200                 205

Thr Pro Ala Thr Asp Cys Ser Asp Gly Asn Tyr Asn Arg Asn Ala Ser
    210                 215                 220

Leu Asn Ser Phe Lys Glu Tyr Phe Asn Leu Arg Asn Cys Thr Phe Met
225                 230                 235                 240

Tyr Thr Tyr Asn Ile Thr Glu Asp Glu Ile Leu Glu Trp Phe Gly Ile
                245                 250                 255
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Thr Gln Thr Ala Gln Gly Val His Leu Phe Ser Ser Arg Tyr Val Asp
            260                 265                 270

Leu Tyr Gly Gly Asn Met Phe Gln Phe Ala Thr Leu Pro Val Tyr Asp
        275                 280                 285

Thr Ile Lys Tyr Tyr Ser Ile Ile Pro His Ser Ile Arg Ser Ile Gln
    290                 295                 300

Ser Asp Arg Lys Ala Trp Ala Ala Phe Tyr Val Tyr Lys Leu Gln Pro
305                 310                 315                 320

Leu Thr Phe Leu Leu Asp Phe Ser Val Asp Gly Tyr Ile Arg Arg Ala
                325                 330                 335

Ile Asp Cys Gly Phe Asn Asp Leu Ser Gln Leu His Cys Ser Tyr Glu
            340                 345                 350

Ser Phe Asp Val Glu Ser Gly Val Tyr Ser Val Ser Ser Phe Glu Ala
        355                 360                 365

Lys Pro Ser Gly Ser Val Val Glu Gln Ala Glu Gly Val Glu Cys Asp
    370                 375                 380

Phe Ser Pro Leu Leu Ser Gly Thr Pro Pro Gln Val Tyr Asn Phe Lys
385                 390                 395                 400

Arg Leu Val Phe Thr Asn Cys Asn Tyr Asn Leu Thr Lys Leu Leu Ser
                405                 410                 415

Leu Phe Ser Val Asn Asp Phe Thr Cys Ser Gln Ile Ser Pro Ala Ala
            420                 425                 430

Ile Ala Ser Asn Cys Tyr Ser Ser Leu Ile Leu Asp Tyr Phe Ser Tyr
        435                 440                 445

Pro Leu Ser Met Lys Ser Asp Leu Ser Val Ser Ser Ala Gly Pro Ile
    450                 455                 460

Ser Gln Phe Asn Tyr Lys Gln Ser Phe Ser Asn Pro Thr Cys Leu Ile
465                 470                 475                 480

Leu Ala Thr Val Pro His Asn Leu Thr Thr Ile Thr Lys Pro Leu Lys
                485                 490                 495

Tyr Ser Tyr Ile Asn Lys Cys Ser Arg Leu Leu Ser Asp Asp Arg Thr
            500                 505                 510

Glu Val Pro Gln Leu Val Asn Ala Asn Gln Tyr Ser Pro Cys Val Ser
        515                 520                 525

Ile Val Pro Ser Thr Val Trp Glu Asp Gly Asp Tyr Tyr Arg Lys Gln
    530                 535                 540

Leu Ser Pro Leu Glu Gly Gly Gly Trp Leu Val Ala Ser Gly Ser Thr
545                 550                 555                 560

Val Ala Met Thr Glu Gln Leu Gln Met Gly Phe Gly Ile Thr Val Gln
                565                 570                 575

Tyr Gly Thr Asp Thr Asn Ser Val Cys Pro Lys Leu Glu Phe Ala Asn
            580                 585                 590

Asp Thr Lys Ile Ala Ser Gln Leu Gly Asn Cys Val Glu Tyr Ser Leu
        595                 600                 605

Tyr Gly Val Ser Gly Arg Gly Val Phe Gln Asn Cys Thr Ala Val Gly
    610                 615                 620

Val Arg Gln Gln Arg Phe Val Tyr Asp Ala Tyr Gln Asn Leu Val Gly
625                 630                 635                 640

Tyr Tyr Ser Asp Asp Gly Asn Tyr Tyr Cys Leu Arg Ala Cys Val Ser
                645                 650                 655

Val Pro Val Ser Val Ile Tyr Asp Lys Glu Thr Lys Thr His Ala Thr
            660                 665                 670
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Leu Phe Gly Ser Val Ala Cys Glu His Ile Ser Ser Thr Met Ser Gln
        675                 680                 685

Tyr Ser Arg Ser Thr Arg Ser Met Leu Lys Arg Arg Asp Ser Thr Tyr
    690                 695                 700

Gly Pro Leu Gln Thr Pro Val Gly Cys Val Leu Gly Leu Val Asn Ser
705                 710                 715                 720

Ser Leu Phe Val Glu Asp Cys Lys Leu Pro Leu Gly Gln Ser Leu Cys
                725                 730                 735

Ala Leu Pro Asp Thr Pro Ser Thr Leu Thr Pro Arg Ser Val Arg Ser
            740                 745                 750

Val Pro Gly Glu Met Arg Leu Ala Ser Ile Ala Phe Asn His Pro Ile
        755                 760                 765

Gln Val Asp Gln Leu Asn Ser Ser Tyr Phe Lys Leu Ser Ile Pro Thr
    770                 775                 780

Asn Phe Ser Phe Gly Val Thr Gln Glu Tyr Ile Gln Thr Thr Ile Gln
785                 790                 795                 800

Lys Val Thr Val Asp Cys Lys Gln Tyr Val Cys Asn Gly Phe Gln Lys
                805                 810                 815

Cys Glu Gln Leu Leu Arg Glu Tyr Gly Gln Phe Cys Ser Lys Ile Asn
            820                 825                 830

Gln Ala Leu His Gly Ala Asn Leu Arg Gln Asp Asp Ser Val Arg Asn
        835                 840                 845

Leu Phe Ala Ser Val Lys Ser Ser Gln Ser Ser Pro Ile Ile Pro Gly
    850                 855                 860

Phe Gly Gly Asp Phe Asn Leu Thr Leu Leu Glu Pro Val Ser Ile Ser
865                 870                 875                 880

Thr Gly Ser Arg Ser Ala Arg Ser Ala Ile Glu Asp Leu Leu Phe Asp
                885                 890                 895

Lys Val Thr Ile Ala Asp Pro Gly Tyr Met Gln Gly Tyr Asp Asp Cys
            900                 905                 910

Met Gln Gln Gly Pro Ala Ser Ala Arg Asp Leu Ile Cys Ala Gln Tyr
        915                 920                 925

Val Ala Gly Tyr Lys Val Leu Pro Pro Leu Met Asp Val Asn Met Glu
    930                 935                 940

Ala Ala Tyr Thr Ser Ser Leu Leu Gly Ser Ile Ala Gly Val Gly Trp
945                 950                 955                 960

Thr Ala Gly Leu Ser Ser Phe Ala Ala Ile Pro Phe Ala Gln Ser Ile
                965                 970                 975

Phe Tyr Arg Leu Asn Gly Val Gly Ile Thr Gln Gln Val Leu Ser Glu
            980                 985                 990

Asn Gln Lys Leu Ile Ala Asn Lys  Phe Asn Gln Ala Leu  Gly Ala Met
        995                 1000                1005

Gln Thr  Gly Phe Thr Thr Thr  Asn Glu Ala Phe Arg  Lys Val Gln
    1010                1015                1020

Asp Ala  Val Asn Asn Asn Ala  Gln Ala Leu Ser Lys  Leu Ala Ser
    1025                1030                1035

Glu Leu  Ser Asn Thr Phe Gly  Ala Ile Ser Ala Ser  Ile Gly Asp
    1040                1045                1050

Ile Ile  Gln Arg Leu Asp Val  Leu Glu Gln Asp Ala  Gln Ile Asp
    1055                1060                1065

Arg Leu  Ile Asn Gly Arg Leu  Thr Thr Leu Asn Ala  Phe Val Ala
    1070                1075                1080

Gln Gln  Leu Val Arg Ser Glu  Ser Ala Ala Leu Ser  Ala Gln Leu
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    1085                1090                1095

Ala Lys  Asp Lys Val Asn Glu  Cys Val Lys Ala Gln  Ser Lys Arg
    1100                1105                1110

Ser Gly  Phe Cys Gly Gln Gly  Thr His Ile Val Ser  Phe Val Val
    1115                1120                1125

Asn Ala  Pro Asn Gly Leu Tyr  Phe Met His Val Gly  Tyr Tyr Pro
    1130                1135                1140

Ser Asn  His Ile Glu Val Val  Ser Ala Tyr Gly Leu  Cys Asp Ala
    1145                1150                1155

Ala Asn  Pro Thr Asn Cys Ile  Ala Pro Val Asn Gly  Tyr Phe Ile
    1160                1165                1170

Lys Thr  Asn Asn Thr Arg Ile  Val Asp Glu Trp Ser  Tyr Thr Gly
    1175                1180                1185

Ser Ser  Phe Tyr Ala Pro Glu  Pro Ile Thr Ser Leu  Asn Thr Lys
    1190                1195                1200

Tyr Val  Ala Pro Gln Val Thr  Tyr Gln Asn Ile Ser  Thr Asn Leu
    1205                1210                1215

Pro Pro  Pro Leu Leu Gly Asn  Ser Thr Gly Ile Asp  Phe Gln Asp
    1220                1225                1230

Glu Leu  Asp Glu Phe Phe Lys  Asn Val Ser Thr Ser  Ile Pro Asn
    1235                1240                1245

Phe Gly  Ser Leu Thr Gln Ile  Asn Thr Thr Leu Leu  Asp Leu Thr
    1250                1255                1260

Tyr Glu  Met Leu Ser Leu Gln  Gln Val Val Lys Ala  Leu Asn Glu
    1265                1270                1275

Ser Tyr  Ile Asp Leu Lys Glu  Leu Gly Asn Tyr Thr  Tyr Tyr Asn
    1280                1285                1290

Lys Trp  Pro Trp Tyr Ile Trp  Leu Gly Phe Ile Ala  Gly Leu Val
    1295                1300                1305

Ala Leu  Ala Leu Cys Val Phe  Phe Ile Leu Cys Cys  Thr Gly Cys
    1310                1315                1320

Gly Thr  Asn Cys Met Gly Lys  Leu Lys Cys Asn Arg  Cys Cys Asp
    1325                1330                1335

Arg Tyr  Glu Glu Tyr Asp Leu  Glu Pro His Lys Val  His Val His
    1340                1345                1350


<210> SEQ ID NO 25
<211> LENGTH: 1353
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 25

Met Ile His Ser Val Phe Leu Leu Met Phe Leu Leu Thr Pro Thr Glu
1               5                  10                  15

Ser Tyr Val Asp Val Gly Pro Asp Ser Val Lys Ser Ala Cys Ile Glu
            20                  25                  30

Val Asp Ile Gln Gln Thr Phe Phe Asp Lys Thr Trp Pro Arg Pro Ile
        35                  40                  45

Asp Val Ser Lys Ala Asp Gly Ile Ile Tyr Pro Gln Gly Arg Thr Tyr
    50                  55                  60

Ser Asn Ile Thr Ile Thr Tyr Gln Gly Leu Phe Pro Tyr Gln Gly Asp
65                  70                  75                  80

His Gly Asp Met Tyr Val Tyr Ser Ala Gly His Ala Thr Gly Thr Thr
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                85                  90                  95

Pro Gln Lys Leu Phe Val Ala Asn Tyr Ser Gln Asp Val Lys Gln Phe
            100                 105                 110

Ala Asn Gly Phe Val Val Arg Ile Gly Ala Ala Ala Asn Ser Thr Gly
        115                 120                 125

Thr Val Ile Ile Ser Pro Ser Thr Ser Ala Thr Ile Arg Lys Ile Tyr
    130                 135                 140

Pro Ala Phe Met Leu Gly Ser Ser Val Gly Asn Phe Ser Asp Gly Lys
145                 150                 155                 160

Met Gly Arg Phe Phe Asn His Thr Leu Val Leu Leu Pro Asp Gly Cys
                165                 170                 175

Gly Thr Leu Leu Arg Ala Phe Tyr Cys Ile Leu Glu Pro Arg Ser Gly
            180                 185                 190

Asn His Cys Pro Ala Gly Asn Ser Tyr Thr Ser Phe Ala Thr Tyr His
        195                 200                 205

Thr Pro Ala Thr Asp Cys Ser Asp Gly Asn Tyr Asn Arg Asn Ala Ser
    210                 215                 220

Leu Asn Ser Phe Lys Glu Tyr Phe Asn Leu Arg Asn Cys Thr Phe Met
225                 230                 235                 240

Tyr Thr Tyr Asn Ile Thr Glu Asp Glu Ile Leu Glu Trp Phe Gly Ile
                245                 250                 255

Thr Gln Thr Ala Gln Gly Val His Leu Phe Ser Ser Arg Tyr Val Asp
            260                 265                 270

Leu Tyr Gly Gly Asn Met Phe Gln Phe Ala Thr Leu Pro Val Tyr Asp
        275                 280                 285

Thr Ile Lys Tyr Tyr Ser Ile Ile Pro His Ser Ile Arg Ser Ile Gln
    290                 295                 300

Ser Asp Arg Lys Ala Trp Ala Ala Phe Tyr Val Tyr Lys Leu Gln Pro
305                 310                 315                 320

Leu Thr Phe Leu Leu Asp Phe Ser Val Asp Gly Tyr Ile Arg Arg Ala
                325                 330                 335

Ile Asp Cys Gly Phe Asn Asp Leu Ser Gln Leu His Cys Ser Tyr Glu
            340                 345                 350

Ser Phe Asp Val Glu Ser Gly Val Tyr Ser Val Ser Ser Phe Glu Ala
        355                 360                 365

Lys Pro Ser Gly Ser Val Val Glu Gln Ala Glu Gly Val Glu Cys Asp
    370                 375                 380

Phe Ser Pro Leu Leu Ser Gly Thr Pro Pro Gln Val Tyr Asn Phe Lys
385                 390                 395                 400

Arg Leu Val Phe Thr Asn Cys Asn Tyr Asn Leu Thr Lys Leu Leu Ser
                405                 410                 415

Leu Phe Ser Val Asn Asp Phe Thr Cys Ser Gln Ile Ser Pro Ala Ala
            420                 425                 430

Ile Ala Ser Asn Cys Tyr Ser Ser Leu Ile Leu Asp Tyr Phe Ser Tyr
        435                 440                 445

Pro Leu Ser Met Lys Ser Asp Leu Ser Val Ser Ser Ala Gly Pro Ile
    450                 455                 460

Ser Gln Phe Asn Tyr Lys Gln Ser Phe Ser Asn Pro Thr Cys Leu Ile
465                 470                 475                 480

Leu Ala Thr Val Pro His Asn Leu Thr Thr Ile Thr Lys Pro Leu Lys
                485                 490                 495

Tyr Ser Tyr Ile Asn Lys Cys Ser Arg Leu Leu Ser Asp Asp Arg Thr
            500                 505                 510
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Glu Val Pro Gln Leu Val Asn Ala Asn Gln Tyr Ser Pro Cys Val Ser
        515                 520                 525

Ile Val Pro Ser Thr Val Trp Glu Asp Gly Asp Tyr Tyr Arg Lys Gln
    530                 535                 540

Leu Ser Pro Leu Glu Gly Gly Gly Trp Leu Val Ala Ser Gly Ser Thr
545                 550                 555                 560

Val Ala Met Thr Glu Gln Leu Gln Met Gly Phe Gly Ile Thr Val Gln
                565                 570                 575

Tyr Gly Thr Asp Thr Asn Ser Val Cys Pro Lys Leu Glu Phe Ala Asn
            580                 585                 590

Asp Thr Lys Ile Ala Ser Gln Leu Gly Asn Cys Val Glu Tyr Ser Leu
        595                 600                 605

Tyr Gly Val Ser Gly Arg Gly Val Phe Gln Asn Cys Thr Ala Val Gly
    610                 615                 620

Val Arg Gln Gln Arg Phe Val Tyr Asp Ala Tyr Gln Asn Leu Val Gly
625                 630                 635                 640

Tyr Tyr Ser Asp Asp Gly Asn Tyr Tyr Cys Leu Arg Ala Cys Val Ser
                645                 650                 655

Val Pro Val Ser Val Ile Tyr Asp Lys Glu Thr Lys Thr His Ala Thr
            660                 665                 670

Leu Phe Gly Ser Val Ala Cys Glu His Ile Ser Ser Thr Met Ser Gln
        675                 680                 685

Tyr Ser Arg Ser Thr Arg Ser Met Leu Lys Arg Arg Asp Ser Thr Tyr
    690                 695                 700

Gly Pro Leu Gln Thr Pro Val Gly Cys Val Leu Gly Leu Val Asn Ser
705                 710                 715                 720

Ser Leu Phe Val Glu Asp Cys Lys Leu Pro Leu Gly Gln Ser Leu Cys
                725                 730                 735

Ala Leu Pro Asp Thr Pro Ser Thr Leu Thr Pro Arg Ser Val Arg Ser
            740                 745                 750

Val Pro Gly Glu Met Arg Leu Ala Ser Ile Ala Phe Asn His Pro Ile
        755                 760                 765

Gln Val Asp Gln Leu Asn Ser Ser Tyr Phe Lys Leu Ser Ile Pro Thr
    770                 775                 780

Asn Phe Ser Phe Gly Val Thr Gln Glu Tyr Ile Gln Thr Thr Ile Gln
785                 790                 795                 800

Lys Val Thr Val Asp Cys Lys Gln Tyr Val Cys Asn Gly Phe Gln Lys
                805                 810                 815

Cys Glu Gln Leu Leu Arg Glu Tyr Gly Gln Phe Cys Ser Lys Ile Asn
            820                 825                 830

Gln Ala Leu His Gly Ala Asn Leu Arg Gln Asp Asp Ser Val Arg Asn
        835                 840                 845

Leu Phe Ala Ser Val Lys Ser Ser Gln Ser Ser Pro Ile Ile Pro Gly
    850                 855                 860

Phe Gly Gly Asp Phe Asn Leu Thr Leu Leu Glu Pro Val Ser Ile Ser
865                 870                 875                 880

Thr Gly Ser Arg Ser Ala Arg Ser Ala Ile Glu Asp Leu Leu Phe Asp
                885                 890                 895

Lys Val Thr Ile Ala Asp Pro Gly Tyr Met Gln Gly Tyr Asp Asp Cys
            900                 905                 910

Met Gln Gln Gly Pro Ala Ser Ala Arg Asp Leu Ile Cys Ala Gln Tyr
        915                 920                 925
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Val Ala Gly Tyr Lys Val Leu Pro Pro Leu Met Asp Val Asn Met Glu
    930                 935                 940

Ala Ala Tyr Thr Ser Ser Leu Leu Gly Ser Ile Ala Gly Val Gly Trp
945                 950                 955                 960

Thr Ala Gly Leu Ser Ser Phe Ala Ala Ile Pro Phe Ala Gln Ser Ile
                965                 970                 975

Phe Tyr Arg Leu Asn Gly Val Gly Ile Thr Gln Gln Val Leu Ser Glu
            980                 985                 990

Asn Gln Lys Leu Ile Ala Asn Lys  Phe Asn Gln Ala Leu  Gly Ala Met
        995                 1000                1005

Gln Thr  Gly Phe Thr Thr Thr  Asn Glu Ala Phe Gln  Lys Val Gln
    1010                1015                1020

Asp Ala  Val Asn Asn Asn Ala  Gln Ala Leu Ser Lys  Leu Ala Ser
    1025                1030                1035

Glu Leu  Ser Asn Thr Phe Gly  Ala Ile Ser Ala Ser  Ile Gly Asp
    1040                1045                1050

Ile Ile  Gln Arg Leu Asp Val  Leu Glu Gln Asp Ala  Gln Ile Asp
    1055                1060                1065

Arg Leu  Ile Asn Gly Arg Leu  Thr Thr Leu Asn Ala  Phe Val Ala
    1070                1075                1080

Gln Gln  Leu Val Arg Ser Glu  Ser Ala Ala Leu Ser  Ala Gln Leu
    1085                1090                1095

Ala Lys  Asp Lys Val Asn Glu  Cys Val Lys Ala Gln  Ser Lys Arg
    1100                1105                1110

Ser Gly  Phe Cys Gly Gln Gly  Thr His Ile Val Ser  Phe Val Val
    1115                1120                1125

Asn Ala  Pro Asn Gly Leu Tyr  Phe Met His Val Gly  Tyr Tyr Pro
    1130                1135                1140

Ser Asn  His Ile Glu Val Val  Ser Ala Tyr Gly Leu  Cys Asp Ala
    1145                1150                1155

Ala Asn  Pro Thr Asn Cys Ile  Ala Pro Val Asn Gly  Tyr Phe Ile
    1160                1165                1170

Lys Thr  Asn Asn Thr Arg Ile  Val Asp Glu Trp Ser  Tyr Thr Gly
    1175                1180                1185

Ser Ser  Phe Tyr Ala Pro Glu  Pro Ile Thr Ser Leu  Asn Thr Lys
    1190                1195                1200

Tyr Val  Ala Pro Gln Val Thr  Tyr Gln Asn Ile Ser  Thr Asn Leu
    1205                1210                1215

Pro Pro  Pro Leu Leu Gly Asn  Ser Thr Gly Ile Asp  Phe Gln Asp
    1220                1225                1230

Glu Leu  Asp Glu Phe Phe Lys  Asn Val Ser Thr Ser  Ile Pro Asn
    1235                1240                1245

Phe Gly  Ser Leu Thr Gln Ile  Asn Thr Thr Leu Leu  Asp Leu Thr
    1250                1255                1260

Tyr Glu  Met Leu Ser Leu Gln  Gln Val Val Lys Ala  Leu Asn Glu
    1265                1270                1275

Ser Tyr  Ile Asp Leu Lys Glu  Leu Gly Asn Tyr Thr  Tyr Tyr Asn
    1280                1285                1290

Lys Trp  Pro Trp Tyr Ile Trp  Leu Gly Phe Ile Ala  Gly Leu Val
    1295                1300                1305

Ala Leu  Ala Leu Cys Val Phe  Phe Ile Leu Cys Cys  Thr Gly Cys
    1310                1315                1320

Gly Thr  Asn Cys Met Gly Lys  Leu Lys Cys Asn Arg  Cys Cys Asp
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    1325                1330                1335

Arg Tyr  Glu Glu Tyr Asp Leu  Glu Pro His Lys Val  His Val His
    1340                1345                1350


<210> SEQ ID NO 26
<211> LENGTH: 615
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 26

Met Ile His Ser Val Phe Leu Leu Met Phe Leu Leu Thr Pro Thr Glu
1               5                   10                  15

Ser Asp Cys Lys Leu Pro Leu Gly Gln Ser Leu Cys Ala Leu Pro Asp
            20                  25                  30

Thr Pro Ser Thr Leu Thr Pro Arg Ser Val Arg Ser Val Pro Gly Glu
        35                  40                  45

Met Arg Leu Ala Ser Ile Ala Phe Asn His Pro Ile Gln Val Asp Gln
    50                  55                  60

Leu Asn Ser Ser Tyr Phe Lys Leu Ser Ile Pro Thr Asn Phe Ser Phe
65                  70                  75                  80

Gly Val Thr Gln Glu Tyr Ile Gln Thr Thr Ile Gln Lys Val Thr Val
                85                  90                  95

Asp Cys Lys Gln Tyr Val Cys Asn Gly Phe Gln Lys Cys Glu Gln Leu
            100                 105                 110

Leu Arg Glu Tyr Gly Gln Phe Cys Ser Lys Ile Asn Gln Ala Leu His
        115                 120                 125

Gly Ala Asn Leu Arg Gln Asp Asp Ser Val Arg Asn Leu Phe Ala Ser
    130                 135                 140

Val Lys Ser Ser Gln Ser Ser Pro Ile Ile Pro Gly Phe Gly Gly Asp
145                 150                 155                 160

Phe Asn Leu Thr Leu Leu Glu Pro Val Ser Ile Ser Thr Gly Ser Arg
                165                 170                 175

Ser Ala Arg Ser Ala Ile Glu Asp Leu Leu Phe Asp Lys Val Thr Ile
            180                 185                 190

Ala Asp Pro Gly Tyr Met Gln Gly Tyr Asp Asp Cys Met Gln Gln Gly
        195                 200                 205

Pro Ala Ser Ala Arg Asp Leu Ile Cys Ala Gln Tyr Val Ala Gly Tyr
    210                 215                 220

Lys Val Leu Pro Pro Leu Met Asp Val Asn Met Glu Ala Ala Tyr Thr
225                 230                 235                 240

Ser Ser Leu Leu Gly Ser Ile Ala Gly Val Gly Trp Thr Ala Gly Leu
                245                 250                 255

Ser Ser Phe Ala Ala Ile Pro Phe Ala Gln Ser Ile Phe Tyr Arg Leu
            260                 265                 270

Asn Gly Val Gly Ile Thr Gln Gln Val Leu Ser Glu Asn Gln Lys Leu
        275                 280                 285

Ile Ala Asn Lys Phe Asn Gln Ala Leu Gly Ala Met Gln Thr Gly Phe
    290                 295                 300

Thr Thr Thr Asn Glu Ala Phe Gln Lys Val Gln Asp Ala Val Asn Asn
305                 310                 315                 320

Asn Ala Gln Ala Leu Ser Lys Leu Ala Ser Glu Leu Ser Asn Thr Phe
                325                 330                 335

Gly Ala Ile Ser Ala Ser Ile Gly Asp Ile Ile Gln Arg Leu Asp Val
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            340                 345                 350

Leu Glu Gln Asp Ala Gln Ile Asp Arg Leu Ile Asn Gly Arg Leu Thr
        355                 360                 365

Thr Leu Asn Ala Phe Val Ala Gln Gln Leu Val Arg Ser Glu Ser Ala
    370                 375                 380

Ala Leu Ser Ala Gln Leu Ala Lys Asp Lys Val Asn Glu Cys Val Lys
385                 390                 395                 400

Ala Gln Ser Lys Arg Ser Gly Phe Cys Gly Gln Gly Thr His Ile Val
                405                 410                 415

Ser Phe Val Val Asn Ala Pro Asn Gly Leu Tyr Phe Met His Val Gly
            420                 425                 430

Tyr Tyr Pro Ser Asn His Ile Glu Val Val Ser Ala Tyr Gly Leu Cys
        435                 440                 445

Asp Ala Ala Asn Pro Thr Asn Cys Ile Ala Pro Val Asn Gly Tyr Phe
    450                 455                 460

Ile Lys Thr Asn Asn Thr Arg Ile Val Asp Glu Trp Ser Tyr Thr Gly
465                 470                 475                 480

Ser Ser Phe Tyr Ala Pro Glu Pro Ile Thr Ser Leu Asn Thr Lys Tyr
                485                 490                 495

Val Ala Pro Gln Val Thr Tyr Gln Asn Ile Ser Thr Asn Leu Pro Pro
            500                 505                 510

Pro Leu Leu Gly Asn Ser Thr Gly Ile Asp Phe Gln Asp Glu Leu Asp
        515                 520                 525

Glu Phe Phe Lys Asn Val Ser Thr Ser Ile Pro Asn Phe Gly Ser Leu
    530                 535                 540

Thr Gln Ile Asn Thr Thr Leu Leu Asp Leu Thr Tyr Glu Met Leu Ser
545                 550                 555                 560

Leu Gln Gln Val Val Lys Ala Leu Asn Glu Ser Tyr Ile Asp Leu Lys
                565                 570                 575

Glu Leu Gly Asn Tyr Thr Tyr Tyr Asn Lys Trp Pro Asp Lys Ile Glu
            580                 585                 590

Glu Ile Leu Ser Lys Ile Tyr His Ile Glu Asn Glu Ile Ala Arg Ile
        595                 600                 605

Lys Lys Leu Ile Gly Glu Ala
    610                 615


<210> SEQ ID NO 27
<211> LENGTH: 1353
<212> TYPE: PRT
<213> ORGANISM: Middle East respiratory syndrome coronavirus

<400> SEQUENCE: 27

Met Ile His Ser Val Phe Leu Leu Met Phe Leu Leu Thr Pro Thr Glu
1               5                   10                  15

Ser Tyr Val Asp Val Gly Pro Asp Ser Val Lys Ser Ala Cys Ile Glu
            20                  25                  30

Val Asp Ile Gln Gln Thr Phe Phe Asp Lys Thr Trp Pro Arg Pro Ile
        35                  40                  45

Asp Val Ser Lys Ala Asp Gly Ile Ile Tyr Pro Gln Gly Arg Thr Tyr
    50                  55                  60

Ser Asn Ile Thr Ile Thr Tyr Gln Gly Leu Phe Pro Tyr Gln Gly Asp
65                  70                  75                  80

His Gly Asp Met Tyr Val Tyr Ser Ala Gly His Ala Thr Gly Thr Thr
                85                  90                  95
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Pro Gln Lys Leu Phe Val Ala Asn Tyr Ser Gln Asp Val Lys Gln Phe
            100                 105                 110

Ala Asn Gly Phe Val Val Arg Ile Gly Ala Ala Ala Asn Ser Thr Gly
        115                 120                 125

Thr Val Ile Ile Ser Pro Ser Thr Ser Ala Thr Ile Arg Lys Ile Tyr
    130                 135                 140

Pro Ala Phe Met Leu Gly Ser Ser Val Gly Asn Phe Ser Asp Gly Lys
145                 150                 155                 160

Met Gly Arg Phe Phe Asn His Thr Leu Val Leu Leu Pro Asp Gly Cys
                165                 170                 175

Gly Thr Leu Leu Arg Ala Phe Tyr Cys Ile Leu Glu Pro Arg Ser Gly
            180                 185                 190

Asn His Cys Pro Ala Gly Asn Ser Tyr Thr Ser Phe Ala Thr Tyr His
        195                 200                 205

Thr Pro Ala Thr Asp Cys Ser Asp Gly Asn Tyr Asn Arg Asn Ala Ser
    210                 215                 220

Leu Asn Ser Phe Lys Glu Tyr Phe Asn Leu Arg Asn Cys Thr Phe Met
225                 230                 235                 240

Tyr Thr Tyr Asn Ile Thr Glu Asp Glu Ile Leu Glu Trp Phe Gly Ile
                245                 250                 255

Thr Gln Thr Ala Gln Gly Val His Leu Phe Ser Ser Arg Tyr Val Asp
            260                 265                 270

Leu Tyr Gly Gly Asn Met Phe Gln Phe Ala Thr Leu Pro Val Tyr Asp
        275                 280                 285

Thr Ile Lys Tyr Tyr Ser Ile Ile Pro His Ser Ile Arg Ser Ile Gln
    290                 295                 300

Ser Asp Arg Lys Ala Trp Ala Ala Phe Tyr Val Tyr Lys Leu Gln Pro
305                 310                 315                 320

Leu Thr Phe Leu Leu Asp Phe Ser Val Asp Gly Tyr Ile Arg Arg Ala
                325                 330                 335

Ile Asp Cys Gly Phe Asn Asp Leu Ser Gln Leu His Cys Ser Tyr Glu
            340                 345                 350

Ser Phe Asp Val Glu Ser Gly Val Tyr Ser Val Ser Ser Phe Glu Ala
        355                 360                 365

Lys Pro Ser Gly Ser Val Val Glu Gln Ala Glu Gly Val Glu Cys Asp
    370                 375                 380

Phe Ser Pro Leu Leu Ser Gly Thr Pro Pro Gln Val Tyr Asn Phe Lys
385                 390                 395                 400

Arg Leu Val Phe Thr Asn Cys Asn Tyr Asn Leu Thr Lys Leu Leu Ser
                405                 410                 415

Leu Phe Ser Val Asn Asp Phe Thr Cys Ser Gln Ile Ser Pro Ala Ala
            420                 425                 430

Ile Ala Ser Asn Cys Tyr Ser Ser Leu Ile Leu Asp Tyr Phe Ser Tyr
        435                 440                 445

Pro Leu Ser Met Lys Ser Asp Leu Ser Val Ser Ser Ala Gly Pro Ile
    450                 455                 460

Ser Gln Phe Asn Tyr Lys Gln Ser Phe Ser Asn Pro Thr Cys Leu Ile
465                 470                 475                 480

Leu Ala Thr Val Pro His Asn Leu Thr Thr Ile Thr Lys Pro Leu Lys
                485                 490                 495

Tyr Ser Tyr Ile Asn Lys Cys Ser Arg Leu Leu Ser Asp Asp Arg Thr
            500                 505                 510

Glu Val Pro Gln Leu Val Asn Ala Asn Gln Tyr Ser Pro Cys Val Ser
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        515                 520                 525

Ile Val Pro Ser Thr Val Trp Glu Asp Gly Asp Tyr Tyr Arg Lys Gln
    530                 535                 540

Leu Ser Pro Leu Glu Gly Gly Gly Trp Leu Val Ala Ser Gly Ser Thr
545                 550                 555                 560

Val Ala Met Thr Glu Gln Leu Gln Met Gly Phe Gly Ile Thr Val Gln
                565                 570                 575

Tyr Gly Thr Asp Thr Asn Ser Val Cys Pro Lys Leu Glu Phe Ala Asn
            580                 585                 590

Asp Thr Lys Ile Ala Ser Gln Leu Gly Asn Cys Val Glu Tyr Ser Leu
        595                 600                 605

Tyr Gly Val Ser Gly Arg Gly Val Phe Gln Asn Cys Thr Ala Val Gly
    610                 615                 620

Val Arg Gln Gln Arg Phe Val Tyr Asp Ala Tyr Gln Asn Leu Val Gly
625                 630                 635                 640

Tyr Tyr Ser Asp Asp Gly Asn Tyr Tyr Cys Leu Arg Ala Cys Val Ser
                645                 650                 655

Val Pro Val Ser Val Ile Tyr Asp Lys Glu Thr Lys Thr His Ala Thr
            660                 665                 670

Leu Phe Gly Ser Val Ala Cys Glu His Ile Ser Ser Thr Met Ser Gln
        675                 680                 685

Tyr Ser Arg Ser Thr Arg Ser Met Leu Lys Arg Arg Asp Ser Thr Tyr
    690                 695                 700

Gly Pro Leu Gln Thr Pro Val Gly Cys Val Leu Gly Leu Val Asn Ser
705                 710                 715                 720

Ser Leu Phe Val Glu Asp Cys Lys Leu Pro Leu Gly Gln Ser Leu Cys
                725                 730                 735

Ala Leu Pro Asp Thr Pro Ser Thr Leu Thr Pro Arg Ser Val Arg Ser
            740                 745                 750

Val Pro Gly Glu Met Arg Leu Ala Ser Ile Ala Phe Asn His Pro Ile
        755                 760                 765

Gln Val Asp Gln Leu Asn Ser Ser Tyr Phe Lys Leu Ser Ile Pro Thr
    770                 775                 780

Asn Phe Ser Phe Gly Val Thr Gln Glu Tyr Ile Gln Thr Thr Ile Gln
785                 790                 795                 800

Lys Val Thr Val Asp Cys Lys Gln Tyr Val Cys Asn Gly Phe Gln Lys
                805                 810                 815

Cys Glu Gln Leu Leu Arg Glu Tyr Gly Gln Phe Cys Ser Lys Ile Asn
            820                 825                 830

Gln Ala Leu His Gly Ala Asn Leu Arg Gln Asp Asp Ser Val Arg Asn
        835                 840                 845

Leu Phe Ala Ser Val Lys Ser Ser Gln Ser Ser Pro Ile Ile Pro Gly
    850                 855                 860

Phe Gly Gly Asp Phe Asn Leu Thr Leu Leu Glu Pro Val Ser Ile Ser
865                 870                 875                 880

Thr Gly Ser Arg Ser Ala Arg Ser Ala Ile Glu Asp Leu Leu Phe Asp
                885                 890                 895

Lys Val Thr Ile Ala Asp Pro Gly Tyr Met Gln Gly Tyr Asp Asp Cys
            900                 905                 910

Met Gln Gln Gly Pro Ala Ser Ala Arg Asp Leu Ile Cys Ala Gln Tyr
        915                 920                 925

Val Ala Gly Tyr Lys Val Leu Pro Pro Leu Met Asp Val Asn Met Glu
    930                 935                 940
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Ala Ala Tyr Thr Ser Ser Leu Leu Gly Ser Ile Ala Gly Val Gly Trp
945                 950                 955                 960

Thr Ala Gly Leu Ser Ser Phe Ala Ala Ile Pro Phe Ala Gln Ser Ile
                965                 970                 975

Phe Tyr Arg Leu Asn Gly Val Gly Ile Thr Gln Gln Val Leu Ser Glu
            980                 985                 990

Asn Gln Lys Leu Ile Ala Asn Lys  Phe Asn Gln Ala Leu  Gly Ala Met
        995                 1000                1005

Gln Thr  Gly Phe Thr Thr Thr  Asn Glu Ala Phe Arg  Lys Val Gln
    1010                1015                1020

Asp Ala  Val Asn Asn Asn Ala  Gln Ala Leu Ser Lys  Leu Ala Ser
    1025                1030                1035

Glu Leu  Ser Asn Thr Phe Gly  Ala Ile Ser Ala Ser  Ile Gly Asp
    1040                1045                1050

Ile Ile  Gln Arg Leu Asp Val  Leu Glu Gln Asp Ala  Gln Ile Asp
    1055                1060                1065

Arg Leu  Ile Asn Gly Arg Leu  Thr Thr Leu Asn Ala  Phe Val Ala
    1070                1075                1080

Gln Gln  Leu Val Arg Ser Glu  Ser Ala Ala Leu Ser  Ala Gln Leu
    1085                1090                1095

Ala Lys  Asp Lys Val Asn Glu  Cys Val Lys Ala Gln  Ser Lys Arg
    1100                1105                1110

Ser Gly  Phe Cys Gly Gln Gly  Thr His Ile Val Ser  Phe Val Val
    1115                1120                1125

Asn Ala  Pro Asn Gly Leu Tyr  Phe Met His Val Gly  Tyr Tyr Pro
    1130                1135                1140

Ser Asn  His Ile Glu Val Val  Ser Ala Tyr Gly Leu  Cys Asp Ala
    1145                1150                1155

Ala Asn  Pro Thr Asn Cys Ile  Ala Pro Val Asn Gly  Tyr Phe Ile
    1160                1165                1170

Lys Thr  Asn Asn Thr Arg Ile  Val Asp Glu Trp Ser  Tyr Thr Gly
    1175                1180                1185

Ser Ser  Phe Tyr Ala Pro Glu  Pro Ile Thr Ser Leu  Asn Thr Lys
    1190                1195                1200

Tyr Val  Ala Pro His Val Thr  Tyr Gln Asn Ile Ser  Thr Asn Leu
    1205                1210                1215

Pro Pro  Pro Leu Leu Gly Asn  Ser Thr Gly Ile Asp  Phe Gln Asp
    1220                1225                1230

Glu Leu  Asp Glu Phe Phe Lys  Asn Val Ser Thr Ser  Ile Pro Asn
    1235                1240                1245

Phe Gly  Ser Leu Thr Gln Ile  Asn Thr Thr Leu Leu  Asp Leu Thr
    1250                1255                1260

Tyr Glu  Met Leu Ser Leu Gln  Gln Val Val Lys Ala  Leu Asn Glu
    1265                1270                1275

Ser Tyr  Ile Asp Leu Lys Glu  Leu Gly Asn Tyr Thr  Tyr Tyr Asn
    1280                1285                1290

Lys Trp  Pro Trp Tyr Ile Trp  Leu Gly Phe Ile Ala  Gly Leu Val
    1295                1300                1305

Ala Leu  Ala Leu Cys Val Phe  Phe Ile Leu Cys Cys  Thr Gly Cys
    1310                1315                1320

Gly Thr  Asn Cys Met Gly Lys  Leu Lys Cys Asn Arg  Cys Cys Asp
    1325                1330                1335
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Arg Tyr  Glu Glu Tyr Asp Leu  Glu Pro His Lys Val  His Val His
    1340                1345                1350


<210> SEQ ID NO 28
<211> LENGTH: 1353
<212> TYPE: PRT
<213> ORGANISM: Middle East respiratory syndrome coronavirus

<400> SEQUENCE: 28

Met Ile His Ser Val Phe Leu Leu Met Phe Leu Leu Thr Pro Thr Glu
1               5                  10                  15

Ser Tyr Val Asp Val Gly Pro Asp Ser Val Lys Ser Ala Cys Ile Glu
            20                  25                  30

Val Asp Ile Gln Gln Thr Phe Phe Asp Lys Thr Trp Pro Arg Pro Ile
        35                  40                  45

Asp Val Ser Lys Ala Asp Gly Ile Ile Tyr Pro Gln Gly Arg Thr Tyr
    50                  55                  60

Ser Asn Ile Thr Ile Thr Tyr Gln Gly Leu Phe Pro Tyr Gln Gly Asp
65                  70                  75                  80

His Gly Asp Met Tyr Val Tyr Ser Ala Gly His Ala Thr Gly Thr Thr
                85                  90                  95

Pro Gln Lys Leu Phe Val Ala Asn Tyr Ser Gln Asp Val Lys Gln Phe
            100                 105                 110

Ala Asn Gly Phe Val Val Arg Ile Gly Ala Ala Ala Asn Ser Thr Gly
        115                 120                 125

Thr Val Ile Ile Ser Pro Ser Thr Ser Ala Thr Ile Arg Lys Ile Tyr
    130                 135                 140

Pro Ala Phe Met Leu Gly Ser Ser Val Gly Asn Phe Ser Asp Gly Lys
145                 150                 155                 160

Met Gly Arg Phe Phe Asn His Thr Leu Val Leu Leu Pro Asp Gly Cys
                165                 170                 175

Gly Thr Leu Leu Arg Ala Phe Tyr Cys Ile Leu Glu Pro Arg Ser Gly
            180                 185                 190

Asn His Cys Pro Ala Gly Asn Ser Tyr Thr Ser Phe Ala Thr Tyr His
        195                 200                 205

Thr Pro Ala Thr Asp Cys Ser Asp Gly Asn Tyr Asn Arg Asn Ala Ser
    210                 215                 220

Leu Asn Ser Phe Lys Glu Tyr Phe Asn Leu Arg Asn Cys Thr Phe Met
225                 230                 235                 240

Tyr Thr Tyr Asn Ile Thr Glu Asp Glu Ile Leu Glu Trp Phe Gly Ile
                245                 250                 255

Thr Gln Thr Ala Gln Gly Val His Leu Phe Ser Ser Arg Tyr Val Asp
            260                 265                 270

Leu Tyr Gly Gly Asn Met Phe Gln Phe Ala Thr Leu Pro Val Tyr Asp
        275                 280                 285

Thr Ile Lys Tyr Tyr Ser Ile Ile Pro His Ser Ile Arg Ser Ile Gln
    290                 295                 300

Ser Asp Arg Lys Ala Trp Ala Ala Phe Tyr Val Tyr Lys Leu Gln Pro
305                 310                 315                 320

Leu Thr Phe Leu Leu Asp Phe Ser Val Asp Gly Tyr Ile Arg Arg Ala
                325                 330                 335

Ile Asp Cys Gly Phe Asn Asp Leu Ser Gln Leu His Cys Ser Tyr Glu
            340                 345                 350

Ser Phe Asp Val Glu Ser Gly Val Tyr Ser Val Ser Ser Phe Glu Ala
        355                 360                 365
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Lys Pro Ser Gly Ser Val Val Glu Gln Ala Glu Gly Val Glu Cys Asp
    370                 375                 380

Phe Ser Pro Leu Leu Ser Gly Thr Pro Pro Gln Val Tyr Asn Phe Lys
385                 390                 395                 400

Arg Leu Val Phe Thr Asn Cys Asn Tyr Asn Leu Thr Lys Leu Leu Ser
                405                 410                 415

Leu Phe Ser Val Asn Asp Phe Thr Cys Ser Gln Ile Ser Pro Ala Ala
            420                 425                 430

Ile Ala Ser Asn Cys Tyr Ser Ser Leu Ile Leu Asp Tyr Phe Ser Tyr
        435                 440                 445

Pro Leu Ser Met Lys Ser Asp Leu Ser Val Ser Ser Ala Gly Pro Ile
    450                 455                 460

Ser Gln Phe Asn Tyr Lys Gln Ser Phe Ser Asn Pro Thr Cys Leu Ile
465                 470                 475                 480

Leu Ala Thr Val Pro His Asn Leu Thr Thr Ile Thr Lys Pro Leu Lys
                485                 490                 495

Tyr Ser Tyr Ile Asn Lys Cys Ser Arg Leu Leu Ser Asp Asp Arg Thr
            500                 505                 510

Glu Val Pro Gln Leu Val Asn Ala Asn Gln Tyr Ser Pro Cys Val Ser
        515                 520                 525

Ile Val Pro Ser Thr Val Trp Glu Asp Gly Asp Tyr Tyr Arg Lys Gln
    530                 535                 540

Leu Ser Pro Leu Glu Gly Gly Gly Trp Leu Val Ala Ser Gly Ser Thr
545                 550                 555                 560

Val Ala Met Thr Glu Gln Leu Gln Met Gly Phe Gly Ile Thr Val Gln
                565                 570                 575

Tyr Gly Thr Asp Thr Asn Ser Val Cys Pro Lys Leu Glu Phe Ala Asn
            580                 585                 590

Asp Thr Lys Ile Ala Ser Gln Leu Gly Asn Cys Val Glu Tyr Ser Leu
        595                 600                 605

Tyr Gly Val Ser Gly Arg Gly Val Phe Gln Asn Cys Thr Ala Val Gly
    610                 615                 620

Val Arg Gln Gln Arg Phe Val Tyr Asp Ala Tyr Gln Asn Leu Val Gly
625                 630                 635                 640

Tyr Tyr Ser Asp Asp Gly Asn Tyr Tyr Cys Leu Arg Ala Cys Val Ser
                645                 650                 655

Val Pro Val Ser Val Ile Tyr Asp Lys Glu Thr Lys Thr His Ala Thr
            660                 665                 670

Leu Phe Gly Ser Val Ala Cys Glu His Ile Ser Ser Thr Met Ser Gln
        675                 680                 685

Tyr Ser Arg Ser Thr Arg Ser Met Leu Lys Arg Arg Asp Ser Thr Tyr
    690                 695                 700

Gly Pro Leu Gln Thr Pro Val Gly Cys Val Leu Gly Leu Val Asn Ser
705                 710                 715                 720

Ser Leu Phe Val Glu Asp Cys Lys Leu Pro Leu Gly Gln Ser Leu Cys
                725                 730                 735

Ala Leu Pro Asp Thr Pro Ser Thr Leu Thr Pro Arg Ser Val Arg Ser
            740                 745                 750

Val Pro Gly Glu Met Arg Leu Ala Ser Ile Ala Phe Asn His Pro Ile
        755                 760                 765

Gln Val Asp Gln Leu Asn Ser Ser Tyr Phe Lys Leu Ser Ile Pro Thr
    770                 775                 780
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Asn Phe Ser Phe Gly Val Thr Gln Glu Tyr Ile Gln Thr Thr Ile Gln
785                 790                 795                 800

Lys Val Thr Val Asp Cys Lys Gln Tyr Val Cys Asn Gly Phe Gln Lys
                805                 810                 815

Cys Glu Gln Leu Leu Arg Glu Tyr Gly Gln Phe Cys Ser Lys Ile Asn
            820                 825                 830

Gln Ala Leu His Gly Ala Asn Leu Arg Gln Asp Asp Ser Val Arg Asn
        835                 840                 845

Leu Phe Ala Ser Val Lys Ser Ser Gln Ser Ser Pro Ile Ile Pro Gly
    850                 855                 860

Phe Gly Gly Asp Phe Asn Leu Thr Leu Leu Glu Pro Val Ser Ile Ser
865                 870                 875                 880

Thr Gly Ser Arg Ser Ala Arg Ser Ala Ile Glu Asp Leu Leu Phe Asp
                885                 890                 895

Lys Val Thr Ile Ala Asp Pro Gly Tyr Met Gln Gly Tyr Asp Asp Cys
            900                 905                 910

Met Gln Gln Gly Pro Ala Ser Ala Arg Asp Leu Ile Cys Ala Gln Tyr
        915                 920                 925

Val Ala Gly Tyr Lys Val Leu Pro Pro Leu Met Asp Val Asn Met Glu
    930                 935                 940

Ala Ala Tyr Thr Ser Ser Leu Leu Gly Ser Ile Ala Gly Val Gly Trp
945                 950                 955                 960

Thr Ala Gly Leu Ser Ser Phe Ala Ala Ile Pro Phe Ala Gln Ser Ile
                965                 970                 975

Phe Tyr Arg Leu Asn Gly Val Gly Ile Thr Gln Gln Val Leu Ser Glu
            980                 985                 990

Asn Gln Lys Leu Ile Ala Asn Lys  Phe Asn Gln Ala Leu  Gly Ala Met
        995                 1000                1005

Gln Thr  Gly Phe Thr Thr Thr  Asn Glu Ala Phe Arg  Lys Val Gln
    1010                1015                1020

Asp Ala  Val Asn Asn Asn Ala  Gln Ala Leu Ser Lys  Leu Ala Ser
    1025                1030                1035

Glu Leu  Ser Asn Thr Phe Gly  Ala Ile Ser Ala Ser  Ile Gly Asp
    1040                1045                1050

Ile Ile  Gln Arg Leu Asp Val  Leu Glu Gln Asp Ala  Gln Ile Asp
    1055                1060                1065

Arg Leu  Ile Asn Gly Arg Leu  Thr Thr Leu Asn Ala  Phe Val Ala
    1070                1075                1080

Gln Gln  Leu Val Arg Ser Glu  Ser Ala Ala Leu Ser  Ala Gln Leu
    1085                1090                1095

Ala Lys  Asp Lys Val Asn Glu  Cys Val Lys Ala Gln  Ser Lys Arg
    1100                1105                1110

Ser Gly  Phe Cys Gly Gln Gly  Thr His Ile Val Ser  Phe Val Val
    1115                1120                1125

Asn Ala  Pro Asn Gly Leu Tyr  Phe Met His Val Gly  Tyr Tyr Pro
    1130                1135                1140

Ser Asn  His Ile Glu Val Val  Ser Ala Tyr Gly Leu  Cys Asp Ala
    1145                1150                1155

Ala Asn  Pro Thr Asn Cys Ile  Ala Pro Val Asn Gly  Tyr Phe Ile
    1160                1165                1170

Lys Thr  Asn Asn Thr Arg Ile  Val Asp Glu Trp Ser  Tyr Thr Gly
    1175                1180                1185

Ser Ser  Phe Tyr Ala Pro Glu  Pro Ile Thr Ser Leu  Asn Thr Lys
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    1190                1195                1200

Tyr Val  Ala Pro His Val Thr  Tyr Gln Asn Ile Ser  Thr Asn Leu
    1205                1210                1215

Pro Pro  Pro Leu Leu Gly Asn  Ser Thr Gly Ile Asp  Phe Gln Asp
    1220                1225                1230

Glu Leu  Asp Glu Phe Phe Lys  Asn Val Ser Thr Ser  Ile Pro Asn
    1235                1240                1245

Phe Gly  Ser Leu Thr Gln Ile  Asn Thr Thr Leu Leu  Asp Leu Thr
    1250                1255                1260

Tyr Glu  Met Leu Ser Leu Gln  Gln Val Val Lys Ala  Leu Asn Glu
    1265                1270                1275

Ser Tyr  Ile Asp Leu Lys Glu  Leu Gly Asn Tyr Thr  Tyr Tyr Asn
    1280                1285                1290

Lys Trp  Pro Trp Tyr Ile Trp  Leu Gly Phe Ile Ala  Gly Leu Val
    1295                1300                1305

Ala Leu  Ala Leu Cys Val Phe  Phe Ile Leu Cys Cys  Thr Gly Cys
    1310                1315                1320

Gly Thr  Asn Cys Met Gly Lys  Leu Lys Cys Asn Arg  Cys Cys Asp
    1325                1330                1335

Arg Tyr  Glu Glu Tyr Asp Leu  Glu Pro His Lys Val  His Val His
    1340                1345                1350


<210> SEQ ID NO 29
<211> LENGTH: 1255
<212> TYPE: PRT
<213> ORGANISM: Human SARS coronavirus

<400> SEQUENCE: 29

Met Phe Ile Phe Leu Leu Phe Leu Thr Leu Thr Ser Gly Ser Asp Leu
1               5                   10                  15

Asp Arg Cys Thr Thr Phe Asp Asp Val Gln Ala Pro Asn Tyr Thr Gln
            20                  25                  30

His Thr Ser Ser Met Arg Gly Val Tyr Tyr Pro Asp Glu Ile Phe Arg
        35                  40                  45

Ser Asp Thr Leu Tyr Leu Thr Gln Asp Leu Phe Leu Pro Phe Tyr Ser
    50                  55                  60

Asn Val Thr Gly Phe His Thr Ile Asn His Thr Phe Gly Asn Pro Val
65                  70                  75                  80

Ile Pro Phe Lys Asp Gly Ile Tyr Phe Ala Ala Thr Glu Lys Ser Asn
                85                  90                  95

Val Val Arg Gly Trp Val Phe Gly Ser Thr Met Asn Asn Lys Ser Gln
            100                 105                 110

Ser Val Ile Ile Ile Asn Asn Ser Thr Asn Val Val Ile Arg Ala Cys
        115                 120                 125

Asn Phe Glu Leu Cys Asp Asn Pro Phe Phe Ala Val Ser Lys Pro Met
    130                 135                 140

Gly Thr Gln Thr His Thr Met Ile Phe Asp Asn Ala Phe Asn Cys Thr
145                 150                 155                 160

Phe Glu Tyr Ile Ser Asp Ala Phe Ser Leu Asp Val Ser Glu Lys Ser
                165                 170                 175

Gly Asn Phe Lys His Leu Arg Glu Phe Val Phe Lys Asn Lys Asp Gly
            180                 185                 190

Phe Leu Tyr Val Tyr Lys Gly Tyr Gln Pro Ile Asp Val Val Arg Asp
        195                 200                 205
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Leu Pro Ser Gly Phe Asn Thr Leu Lys Pro Ile Phe Lys Leu Pro Leu
    210                 215                 220

Gly Ile Asn Ile Thr Asn Phe Arg Ala Ile Leu Thr Ala Phe Ser Pro
225                 230                 235                 240

Ala Gln Asp Ile Trp Gly Thr Ser Ala Ala Ala Tyr Phe Val Gly Tyr
                245                 250                 255

Leu Lys Pro Thr Thr Phe Met Leu Lys Tyr Asp Glu Asn Gly Thr Ile
            260                 265                 270

Thr Asp Ala Val Asp Cys Ser Gln Asn Pro Leu Ala Glu Leu Lys Cys
        275                 280                 285

Ser Val Lys Ser Phe Glu Ile Asp Lys Gly Ile Tyr Gln Thr Ser Asn
    290                 295                 300

Phe Arg Val Val Pro Ser Gly Asp Val Val Arg Phe Pro Asn Ile Thr
305                 310                 315                 320

Asn Leu Cys Pro Phe Gly Glu Val Phe Asn Ala Thr Lys Phe Pro Ser
                325                 330                 335

Val Tyr Ala Trp Glu Arg Lys Lys Ile Ser Asn Cys Val Ala Asp Tyr
            340                 345                 350

Ser Val Leu Tyr Asn Ser Thr Phe Phe Ser Thr Phe Lys Cys Tyr Gly
        355                 360                 365

Val Ser Ala Thr Lys Leu Asn Asp Leu Cys Phe Ser Asn Val Tyr Ala
    370                 375                 380

Asp Ser Phe Val Val Lys Gly Asp Asp Val Arg Gln Ile Ala Pro Gly
385                 390                 395                 400

Gln Thr Gly Val Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe
                405                 410                 415

Met Gly Cys Val Leu Ala Trp Asn Thr Arg Asn Ile Asp Ala Thr Ser
            420                 425                 430

Thr Gly Asn Tyr Asn Tyr Lys Tyr Arg Tyr Leu Arg His Gly Lys Leu
        435                 440                 445

Arg Pro Phe Glu Arg Asp Ile Ser Asn Val Pro Phe Ser Pro Asp Gly
    450                 455                 460

Lys Pro Cys Thr Pro Pro Ala Leu Asn Cys Tyr Trp Pro Leu Asn Asp
465                 470                 475                 480

Tyr Gly Phe Tyr Thr Thr Thr Gly Ile Gly Tyr Gln Pro Tyr Arg Val
                485                 490                 495

Val Val Leu Ser Phe Glu Leu Leu Asn Ala Pro Ala Thr Val Cys Gly
            500                 505                 510

Pro Lys Leu Ser Thr Asp Leu Ile Lys Asn Gln Cys Val Asn Phe Asn
        515                 520                 525

Phe Asn Gly Leu Thr Gly Thr Gly Val Leu Thr Pro Ser Ser Lys Arg
    530                 535                 540

Phe Gln Pro Phe Gln Gln Phe Gly Arg Asp Val Ser Asp Phe Thr Asp
545                 550                 555                 560

Ser Val Arg Asp Pro Lys Thr Ser Glu Ile Leu Asp Ile Ser Pro Cys
                565                 570                 575

Ser Phe Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Ala Ser Ser
            580                 585                 590

Glu Val Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Asp Val Ser Thr
        595                 600                 605

Ala Ile His Ala Asp Gln Leu Thr Pro Ala Trp Arg Ile Tyr Ser Thr
    610                 615                 620

Gly Asn Asn Val Phe Gln Thr Gln Ala Gly Cys Leu Ile Gly Ala Glu
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625 630 635 640

His Val Asp Thr Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile
645 650 655

Cys Ala Ser Tyr His Thr Val Ser Leu Leu Arg Ser Thr Ser Gln Lys
660 665 670

Ser Ile Val Ala Tyr Thr Met Ser Leu Gly Ala Asp Ser Ser Ile Ala
675 680 685

Tyr Ser Asn Asn Thr Ile Ala Ile Pro Thr Asn Phe Ser Ile Ser Ile
690 695 700

Thr Thr Glu Val Met Pro Val Ser Met Ala Lys Thr Ser Val Asp Cys
705 710 715 720

Asn Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ala Asn Leu Leu Leu
725 730 735

Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Ser Gly Ile
740 745 750

Ala Ala Glu Gln Asp Arg Asn Thr Arg Glu Val Phe Ala Gln Val Lys
755 760 765

Gln Met Tyr Lys Thr Pro Thr Leu Lys Tyr Phe Gly Gly Phe Asn Phe
770 775 780

Ser Gln Ile Leu Pro Asp Pro Leu Lys Pro Thr Lys Arg Ser Phe Ile
785 790 795 800

Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Met
805 810 815

Lys Gln Tyr Gly Glu Cys Leu Gly Asp Ile Asn Ala Arg Asp Leu Ile
820 825 830

Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr
835 840 845

Asp Asp Met Ile Ala Ala Tyr Thr Ala Ala Leu Val Ser Gly Thr Ala
850 855 860

Thr Ala Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe
865 870 875 880

Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn
885 890 895

Val Leu Tyr Glu Asn Gln Lys Gln Ile Ala Asn Gln Phe Asn Lys Ala
900 905 910

Ile Ser Gln Ile Gln Glu Ser Leu Thr Thr Thr Ser Thr Ala Leu Gly
915 920 925

Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu
930 935 940

Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn
945 950 955 960

Asp Ile Leu Ser Arg Leu Asp Lys Val Glu Ala Glu Val Gln Ile Asp
965 970 975

Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln
980 985 990

Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala
995 1000 1005

Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp
1010 1015 1020

Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ala Ala
1025 1030 1035

Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ser Gln
1040 1045 1050

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Glu Arg  Asn Phe Thr Thr Ala  Pro Ala Ile Cys His  Glu Gly Lys
    1055                 1060                 1065

Ala Tyr  Phe Pro Arg Glu Gly  Val Phe Val Phe Asn  Gly Thr Ser
    1070                 1075                 1080

Trp Phe  Ile Thr Gln Arg Asn  Phe Phe Ser Pro Gln  Ile Ile Thr
    1085                 1090                 1095

Thr Asp  Asn Thr Phe Val Ser  Gly Asn Cys Asp Val  Val Ile Gly
    1100                 1105                 1110

Ile Ile  Asn Asn Thr Val Tyr  Asp Pro Leu Gln Pro  Glu Leu Asp
    1115                 1120                 1125

Ser Phe  Lys Glu Glu Leu Asp  Lys Tyr Phe Lys Asn  His Thr Ser
    1130                 1135                 1140

Pro Asp  Val Asp Leu Gly Asp  Ile Ser Gly Ile Asn  Ala Ser Val
    1145                 1150                 1155

Val Asn  Ile Gln Lys Glu Ile  Asp Arg Leu Asn Glu  Val Ala Lys
    1160                 1165                 1170

Asn Leu  Asn Glu Ser Leu Ile  Asp Leu Gln Glu Leu  Gly Lys Tyr
    1175                 1180                 1185

Glu Gln  Tyr Ile Lys Trp Pro  Trp Tyr Val Trp Leu  Gly Phe Ile
    1190                 1195                 1200

Ala Gly  Leu Ile Ala Ile Val  Met Val Thr Ile Leu  Leu Cys Cys
    1205                 1210                 1215

Met Thr  Ser Cys Cys Ser Cys  Leu Lys Gly Ala Cys  Ser Cys Gly
    1220                 1225                 1230

Ser Cys  Cys Lys Phe Asp Glu  Asp Asp Ser Glu Pro  Val Leu Lys
    1235                 1240                 1245

Gly Val  Lys Leu His Tyr Thr
    1250                 1255


<210> SEQ ID NO 30
<211> LENGTH: 1353
<212> TYPE: PRT
<213> ORGANISM: Human coronavirus

<400> SEQUENCE: 30

Met Phe Leu Ile Leu Leu Ile Ser Leu Pro Thr Ala Phe Ala Val Ile
1               5                  10                  15

Gly Asp Leu Lys Cys Thr Ser Asp Asn Ile Asn Asp Lys Asp Thr Gly
            20                  25                  30

Pro Pro Pro Ile Ser Thr Asp Thr Val Asp Val Thr Asn Gly Leu Gly
        35                  40                  45

Thr Tyr Tyr Val Leu Asp Arg Val Tyr Leu Asn Thr Thr Leu Phe Leu
    50                  55                  60

Asn Gly Tyr Tyr Pro Thr Ser Gly Ser Thr Tyr Arg Asn Met Ala Leu
65                  70                  75                  80

Lys Gly Ser Val Leu Leu Ser Arg Leu Trp Phe Lys Pro Pro Phe Leu
                85                  90                  95

Ser Asp Phe Ile Asn Gly Ile Phe Ala Lys Val Lys Asn Thr Lys Val
            100                 105                 110

Ile Lys Asp Arg Val Met Tyr Ser Glu Phe Pro Ala Ile Thr Ile Gly
        115                 120                 125

Ser Thr Phe Val Asn Thr Ser Tyr Ser Val Val Val Gln Pro Arg Thr
    130                 135                 140

Ile Asn Ser Thr Gln Asp Gly Asp Asn Lys Leu Gln Gly Leu Leu Glu
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145                 150                 155                 160

Val Ser Val Cys Gln Tyr Asn Met Cys Glu Tyr Pro Gln Thr Ile Cys
                165                 170                 175

His Pro Asn Leu Gly Asn His Arg Lys Glu Leu Trp His Leu Asp Thr
            180                 185                 190

Gly Val Val Ser Cys Leu Tyr Lys Arg Asn Phe Thr Tyr Asp Val Asn
        195                 200                 205

Ala Asp Tyr Leu Tyr Phe His Phe Tyr Gln Glu Gly Gly Thr Phe Tyr
    210                 215                 220

Ala Tyr Phe Thr Asp Thr Gly Val Val Thr Lys Phe Leu Phe Asn Val
225                 230                 235                 240

Tyr Leu Gly Met Ala Leu Ser His Tyr Tyr Val Met Pro Leu Thr Cys
                245                 250                 255

Asn Ser Lys Leu Thr Leu Glu Tyr Trp Val Thr Pro Leu Thr Ser Arg
            260                 265                 270

Gln Tyr Leu Leu Ala Phe Asn Gln Asp Gly Ile Ile Phe Asn Ala Glu
        275                 280                 285

Asp Cys Met Ser Asp Phe Met Ser Glu Ile Lys Cys Lys Thr Gln Ser
    290                 295                 300

Ile Ala Pro Pro Thr Gly Val Tyr Glu Leu Asn Gly Tyr Thr Val Gln
305                 310                 315                 320

Pro Ile Ala Asp Val Tyr Arg Arg Lys Pro Asn Leu Pro Asn Cys Asn
                325                 330                 335

Ile Glu Ala Trp Leu Asn Asp Lys Ser Val Pro Ser Pro Leu Asn Trp
            340                 345                 350

Glu Arg Lys Thr Phe Ser Asn Cys Asn Phe Asn Met Ser Ser Leu Met
        355                 360                 365

Ser Phe Ile Gln Ala Asp Ser Phe Thr Cys Asn Asn Ile Asp Ala Ala
    370                 375                 380

Lys Ile Tyr Gly Met Cys Phe Ser Ser Ile Thr Ile Asp Lys Phe Ala
385                 390                 395                 400

Ile Pro Asn Gly Arg Lys Val Asp Leu Gln Leu Gly Asn Leu Gly Tyr
                405                 410                 415

Leu Gln Ser Phe Asn Tyr Arg Ile Asp Thr Thr Ala Thr Ser Cys Gln
            420                 425                 430

Leu Tyr Tyr Asn Leu Pro Ala Ala Asn Val Ser Val Ser Arg Phe Asn
        435                 440                 445

Pro Ser Thr Trp Asn Lys Arg Phe Gly Phe Ile Glu Asp Ser Val Phe
    450                 455                 460

Lys Pro Arg Pro Ala Gly Val Leu Thr Asn His Asp Val Val Tyr Ala
465                 470                 475                 480

Gln His Cys Phe Lys Ala Pro Lys Asn Phe Cys Pro Cys Lys Leu Asn
                485                 490                 495

Gly Ser Cys Val Gly Ser Gly Pro Gly Lys Asn Asn Gly Ile Gly Thr
            500                 505                 510

Cys Pro Ala Gly Thr Asn Tyr Leu Thr Cys Asp Asn Leu Cys Thr Pro
        515                 520                 525

Asp Pro Ile Thr Phe Thr Gly Thr Tyr Lys Cys Pro Gln Thr Lys Ser
    530                 535                 540

Leu Val Gly Ile Gly Glu His Cys Ser Gly Leu Ala Val Lys Ser Asp
545                 550                 555                 560

Tyr Cys Gly Gly Asn Ser Cys Thr Cys Arg Pro Gln Ala Phe Leu Gly
                565                 570                 575
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Trp Ser Ala Asp Ser Cys Leu Gln Gly Asp Lys Cys Asn Ile Phe Ala
            580                 585                 590

Asn Phe Ile Leu His Asp Val Asn Ser Gly Leu Thr Cys Ser Thr Asp
        595                 600                 605

Leu Gln Lys Ala Asn Thr Asp Ile Ile Leu Gly Val Cys Val Asn Tyr
    610                 615                 620

Asp Leu Tyr Gly Ile Leu Gly Gln Gly Ile Phe Val Glu Val Asn Ala
625                 630                 635                 640

Thr Tyr Tyr Asn Ser Trp Gln Asn Leu Leu Tyr Asp Ser Asn Gly Asn
                645                 650                 655

Leu Tyr Gly Phe Arg Asp Tyr Ile Ile Asn Arg Thr Phe Met Ile Arg
            660                 665                 670

Ser Cys Tyr Ser Gly Arg Val Ser Ala Ala Phe His Ala Asn Ser Ser
        675                 680                 685

Glu Pro Ala Leu Leu Phe Arg Asn Ile Lys Cys Asn Tyr Val Phe Asn
    690                 695                 700

Asn Ser Leu Thr Arg Gln Leu Gln Pro Ile Asn Tyr Phe Asp Ser Tyr
705                 710                 715                 720

Leu Gly Cys Val Val Asn Ala Tyr Asn Ser Thr Ala Ile Ser Val Gln
                725                 730                 735

Thr Cys Asp Leu Thr Val Gly Ser Gly Tyr Cys Val Asp Tyr Ser Lys
            740                 745                 750

Asn Arg Arg Ser Arg Gly Ala Ile Thr Thr Gly Tyr Arg Phe Thr Asn
        755                 760                 765

Phe Glu Pro Phe Thr Val Asn Ser Val Asn Asp Ser Leu Glu Pro Val
    770                 775                 780

Gly Gly Leu Tyr Glu Ile Gln Ile Pro Ser Glu Phe Thr Ile Gly Asn
785                 790                 795                 800

Met Val Glu Phe Ile Gln Thr Ser Ser Pro Lys Val Thr Ile Asp Cys
                805                 810                 815

Ala Ala Phe Val Cys Gly Asp Tyr Ala Ala Cys Lys Ser Gln Leu Val
            820                 825                 830

Glu Tyr Gly Ser Phe Cys Asp Asn Ile Asn Ala Ile Leu Thr Glu Val
        835                 840                 845

Asn Glu Leu Leu Asp Thr Thr Gln Leu Gln Val Ala Asn Ser Leu Met
    850                 855                 860

Asn Gly Val Thr Leu Ser Thr Lys Leu Lys Asp Gly Val Asn Phe Asn
865                 870                 875                 880

Val Asp Asp Ile Asn Phe Ser Pro Val Leu Gly Cys Leu Gly Ser Glu
                885                 890                 895

Cys Ser Lys Ala Ser Ser Arg Ser Ala Ile Glu Asp Leu Leu Phe Asp
            900                 905                 910

Lys Val Lys Leu Ser Asp Val Gly Phe Val Glu Ala Tyr Asn Asn Cys
        915                 920                 925

Thr Gly Gly Ala Glu Ile Arg Asp Leu Ile Cys Val Gln Ser Tyr Lys
    930                 935                 940

Gly Ile Lys Val Leu Pro Pro Leu Leu Ser Glu Asn Gln Ile Ser Gly
945                 950                 955                 960

Tyr Thr Leu Ala Ala Thr Ser Ala Ser Leu Phe Pro Pro Trp Thr Ala
                965                 970                 975

Ala Ala Gly Val Pro Phe Tyr Leu Asn Val Gln Tyr Arg Ile Asn Gly
            980                 985                 990
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Leu Gly Val Thr Met Asp Val Leu  Ser Gln Asn Gln Lys  Leu Ile Ala
        995                1000                1005

Asn Ala  Phe Asn Asn Ala Leu  Tyr Ala Ile Gln Glu  Gly Phe Asp
    1010                1015                1020

Ala Thr  Asn Ser Ala Leu Val  Lys Ile Gln Ala Val  Val Asn Ala
    1025                1030                1035

Asn Ala  Glu Ala Leu Asn Asn  Leu Leu Gln Gln Leu  Ser Asn Arg
    1040                1045                1050

Phe Gly  Ala Ile Ser Ala Ser  Leu Gln Glu Ile Leu  Ser Arg Leu
    1055                1060                1065

Asp Ala  Leu Glu Ala Glu Ala  Gln Ile Asp Arg Leu  Ile Asn Gly
    1070                1075                1080

Arg Leu  Thr Ala Leu Asn Ala  Tyr Val Ser Gln Gln  Leu Ser Asp
    1085                1090                1095

Ser Thr  Leu Val Lys Phe Ser  Ala Ala Gln Ala Met  Glu Lys Val
    1100                1105                1110

Asn Glu  Cys Val Lys Ser Gln  Ser Ser Arg Ile Asn  Phe Cys Gly
    1115                1120                1125

Asn Gly  Asn His Ile Ile Ser  Leu Val Gln Asn Ala  Pro Tyr Gly
    1130                1135                1140

Leu Tyr  Phe Ile His Phe Ser  Tyr Val Pro Thr Lys  Tyr Val Thr
    1145                1150                1155

Ala Arg  Val Ser Pro Gly Leu  Cys Ile Ala Gly Asp  Arg Gly Ile
    1160                1165                1170

Ala Pro  Lys Ser Gly Tyr Phe  Val Asn Val Asn Asn  Thr Trp Met
    1175                1180                1185

Tyr Thr  Gly Ser Gly Tyr Tyr  Tyr Pro Glu Pro Ile  Thr Glu Asn
    1190                1195                1200

Asn Val  Val Val Met Ser Thr  Cys Ala Val Asn Tyr  Thr Lys Ala
    1205                1210                1215

Pro Tyr  Val Met Leu Asn Thr  Ser Ile Pro Asn Leu  Pro Asp Phe
    1220                1225                1230

Lys Glu  Glu Leu Asp Gln Trp  Phe Lys Asn Gln Thr  Ser Val Ala
    1235                1240                1245

Pro Asp  Leu Ser Leu Asp Tyr  Ile Asn Val Thr Phe  Leu Asp Leu
    1250                1255                1260

Gln Val  Glu Met Asn Arg Leu  Gln Glu Ala Ile Lys  Val Leu Asn
    1265                1270                1275

Gln Ser  Tyr Ile Asn Leu Lys  Asp Ile Gly Thr Tyr  Glu Tyr Tyr
    1280                1285                1290

Val Lys  Trp Pro Trp Tyr Val  Trp Leu Leu Ile Cys  Leu Ala Gly
    1295                1300                1305

Val Ala  Met Leu Val Leu Leu  Phe Phe Ile Cys Cys  Cys Thr Gly
    1310                1315                1320

Cys Gly  Thr Ser Cys Phe Lys  Lys Cys Gly Gly Cys  Cys Asp Asp
    1325                1330                1335

Tyr Thr  Gly Tyr Gln Glu Leu  Val Ile Lys Thr Ser  His Asp Asp
    1340                1345                1350


<210> SEQ ID NO 31
<211> LENGTH: 1351
<212> TYPE: PRT
<213> ORGANISM: Human coronavirus

<400> SEQUENCE: 31
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Met Phe Leu Ile Ile Phe Ile Leu Pro Thr Thr Leu Ala Val Ile Gly
1               5                  10                  15

Asp Phe Asn Cys Thr Asn Ser Phe Ile Asn Asp Tyr Asn Lys Thr Ile
            20                  25                  30

Pro Arg Ile Ser Glu Asp Val Val Asp Val Ser Leu Gly Leu Gly Thr
        35                  40                  45

Tyr Tyr Val Leu Asn Arg Val Tyr Leu Asn Thr Thr Leu Leu Phe Thr
    50                  55                  60

Gly Tyr Phe Pro Lys Ser Gly Ala Asn Phe Arg Asp Leu Ala Leu Lys
65                  70                  75                  80

Gly Ser Ile Tyr Leu Ser Thr Leu Trp Tyr Lys Pro Pro Phe Leu Ser
                85                  90                  95

Asp Phe Asn Asn Gly Ile Phe Ser Lys Val Lys Asn Thr Lys Leu Tyr
            100                 105                 110

Val Asn Asn Thr Leu Tyr Ser Glu Phe Ser Thr Ile Val Ile Gly Ser
        115                 120                 125

Val Phe Val Asn Thr Ser Tyr Thr Ile Val Val Gln Pro His Asn Gly
    130                 135                 140

Ile Leu Glu Ile Thr Ala Cys Gln Tyr Thr Met Cys Glu Tyr Pro His
145                 150                 155                 160

Thr Val Cys Lys Ser Lys Gly Ser Ile Arg Asn Glu Ser Trp His Ile
                165                 170                 175

Asp Ser Ser Glu Pro Leu Cys Leu Phe Lys Lys Asn Phe Thr Tyr Asn
            180                 185                 190

Val Ser Ala Asp Trp Leu Tyr Phe His Phe Tyr Gln Glu Arg Gly Val
        195                 200                 205

Phe Tyr Ala Tyr Tyr Ala Asp Val Gly Met Pro Thr Thr Phe Leu Phe
    210                 215                 220

Ser Leu Tyr Leu Gly Thr Ile Leu Ser His Tyr Tyr Val Met Pro Leu
225                 230                 235                 240

Thr Cys Asn Ala Ile Ser Ser Asn Thr Asp Asn Glu Thr Leu Glu Tyr
                245                 250                 255

Trp Val Thr Pro Leu Ser Arg Arg Gln Tyr Leu Leu Asn Phe Asp Glu
            260                 265                 270

His Gly Val Ile Thr Asn Ala Val Asp Cys Ser Ser Ser Phe Leu Ser
        275                 280                 285

Glu Ile Gln Cys Lys Thr Gln Ser Phe Ala Pro Asn Thr Gly Val Tyr
    290                 295                 300

Asp Leu Ser Gly Phe Thr Val Lys Pro Val Ala Thr Val Tyr Arg Arg
305                 310                 315                 320

Ile Pro Asn Leu Pro Asp Cys Asp Ile Asp Asn Trp Leu Asn Asn Val
                325                 330                 335

Ser Val Pro Ser Pro Leu Asn Trp Glu Arg Arg Ile Phe Ser Asn Cys
            340                 345                 350

Asn Phe Asn Leu Ser Thr Leu Leu Arg Leu Val His Val Asp Ser Phe
        355                 360                 365

Ser Cys Asn Asn Leu Asp Lys Ser Lys Ile Phe Gly Ser Cys Phe Asn
    370                 375                 380

Ser Ile Thr Val Asp Lys Phe Ala Ile Pro Asn Arg Arg Arg Asp Asp
385                 390                 395                 400

Leu Gln Leu Gly Ser Ser Gly Phe Leu Gln Ser Ser Asn Tyr Lys Ile
                405                 410                 415
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Asp Ile Ser Ser Ser Ser Cys Gln Leu Tyr Tyr Ser Leu Pro Leu Val
            420                 425                 430

Asn Val Thr Ile Asn Asn Phe Asn Pro Ser Ser Trp Asn Arg Arg Tyr
        435                 440                 445

Gly Phe Gly Ser Phe Asn Leu Ser Ser Tyr Asp Val Val Tyr Ser Asp
    450                 455                 460

His Cys Phe Ser Val Asn Ser Asp Phe Cys Pro Cys Ala Asp Pro Ser
465                 470                 475                 480

Val Val Asn Ser Cys Ala Lys Ser Lys Pro Pro Ser Ala Ile Cys Pro
                485                 490                 495

Ala Gly Thr Lys Tyr Arg His Cys Asp Leu Asp Thr Thr Leu Tyr Val
            500                 505                 510

Lys Asn Trp Cys Arg Cys Ser Cys Leu Pro Asp Pro Ile Ser Thr Tyr
        515                 520                 525

Ser Pro Asn Thr Cys Pro Gln Lys Lys Val Val Val Gly Ile Gly Glu
    530                 535                 540

His Cys Pro Gly Leu Gly Ile Asn Glu Glu Lys Cys Gly Thr Gln Leu
545                 550                 555                 560

Asn His Ser Ser Cys Phe Cys Ser Pro Asp Ala Phe Leu Gly Trp Ser
                565                 570                 575

Phe Asp Ser Cys Ile Ser Asn Asn Arg Cys Asn Ile Phe Ser Asn Phe
            580                 585                 590

Ile Phe Asn Gly Ile Asn Ser Gly Thr Thr Cys Ser Asn Asp Leu Leu
        595                 600                 605

Tyr Ser Asn Thr Glu Ile Ser Thr Gly Val Cys Val Asn Tyr Asp Leu
    610                 615                 620

Tyr Gly Ile Thr Gly Gln Gly Ile Phe Lys Glu Val Ser Ala Ala Tyr
625                 630                 635                 640

Tyr Asn Asn Trp Gln Asn Leu Leu Tyr Asp Ser Asn Gly Asn Ile Ile
                645                 650                 655

Gly Phe Lys Asp Phe Leu Thr Asn Lys Thr Tyr Thr Ile Leu Pro Cys
            660                 665                 670

Tyr Ser Gly Arg Val Ser Ala Ala Phe Tyr Gln Asn Ser Ser Ser Pro
        675                 680                 685

Ala Leu Leu Tyr Arg Asn Leu Lys Cys Ser Tyr Val Leu Asn Asn Ile
    690                 695                 700

Ser Phe Ile Ser Gln Pro Phe Tyr Phe Asp Ser Tyr Leu Gly Cys Val
705                 710                 715                 720

Leu Asn Ala Val Asn Leu Thr Ser Tyr Ser Val Ser Ser Cys Asp Leu
                725                 730                 735

Arg Met Gly Ser Gly Phe Cys Ile Asp Tyr Ala Leu Pro Ser Ser Arg
            740                 745                 750

Arg Lys Arg Arg Gly Ile Ser Ser Pro Tyr Arg Phe Val Thr Phe Glu
        755                 760                 765

Pro Phe Asn Val Ser Phe Val Asn Asp Ser Val Glu Thr Val Gly Gly
    770                 775                 780

Leu Phe Glu Ile Gln Ile Pro Thr Asn Phe Thr Ile Ala Gly His Glu
785                 790                 795                 800

Glu Phe Ile Gln Thr Ser Ser Pro Lys Val Thr Ile Asp Cys Ser Ala
                805                 810                 815

Phe Val Cys Ser Asn Tyr Ala Ala Cys His Asp Leu Leu Ser Glu Tyr
            820                 825                 830

Gly Thr Phe Cys Asp Asn Ile Asn Ser Ile Leu Asn Glu Val Asn Asp
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        835                 840                 845

Leu Leu Asp Ile Thr Gln Leu Gln Val Ala Asn Ala Leu Met Gln Gly
    850                 855                 860

Val Thr Leu Ser Ser Asn Leu Asn Thr Asn Leu His Ser Asp Val Asp
865                 870                 875                 880

Asn Ile Asp Phe Lys Ser Leu Leu Gly Cys Leu Gly Ser Gln Cys Gly
                885                 890                 895

Ser Ser Ser Arg Ser Leu Leu Glu Asp Leu Leu Phe Asn Lys Val Lys
            900                 905                 910

Leu Ser Asp Val Gly Phe Val Glu Ala Tyr Asn Asn Cys Thr Gly Gly
        915                 920                 925

Ser Glu Ile Arg Asp Leu Leu Cys Val Gln Ser Phe Asn Gly Ile Lys
    930                 935                 940

Val Leu Pro Pro Ile Leu Ser Glu Thr Gln Ile Ser Gly Tyr Thr Thr
945                 950                 955                 960

Ala Ala Thr Val Ala Ala Met Phe Pro Pro Trp Ser Ala Ala Ala Gly
                965                 970                 975

Val Pro Phe Ser Leu Asn Val Gln Tyr Arg Ile Asn Gly Leu Gly Val
            980                 985                 990

Thr Met Asp Val Leu Asn Lys Asn  Gln Lys Leu Ile Ala  Asn Ala Phe
        995                 1000                1005

Asn Lys  Ala Leu Leu Ser Ile  Gln Asn Gly Phe Thr  Ala Thr Asn
    1010                1015                1020

Ser Ala  Leu Ala Lys Ile Gln  Ser Val Val Asn Ala  Asn Ala Gln
    1025                1030                1035

Ala Leu  Asn Ser Leu Leu Gln  Gln Leu Phe Asn Lys  Phe Gly Ala
    1040                1045                1050

Ile Ser  Ser Ser Leu Gln Glu  Ile Leu Ser Arg Leu  Asp Asn Leu
    1055                1060                1065

Glu Ala  Gln Val Gln Ile Asp  Arg Leu Ile Asn Gly  Arg Leu Thr
    1070                1075                1080

Ala Leu  Asn Ala Tyr Val Ser  Gln Gln Leu Ser Asp  Ile Thr Leu
    1085                1090                1095

Ile Lys  Ala Gly Ala Ser Arg  Ala Ile Glu Lys Val  Asn Glu Cys
    1100                1105                1110

Val Lys  Ser Gln Ser Pro Arg  Ile Asn Phe Cys Gly  Asn Gly Asn
    1115                1120                1125

His Ile  Leu Ser Leu Val Gln  Asn Ala Pro Tyr Gly  Leu Leu Phe
    1130                1135                1140

Ile His  Phe Ser Tyr Lys Pro  Thr Ser Phe Lys Thr  Val Leu Val
    1145                1150                1155

Ser Pro  Gly Leu Cys Leu Ser  Gly Asp Arg Gly Ile  Ala Pro Lys
    1160                1165                1170

Gln Gly  Tyr Phe Ile Lys Gln  Asn Asp Ser Trp Met  Phe Thr Gly
    1175                1180                1185

Ser Ser  Tyr Tyr Tyr Pro Glu  Pro Ile Ser Asp Lys  Asn Val Val
    1190                1195                1200

Phe Met  Asn Ser Cys Ser Val  Asn Phe Thr Lys Ala  Pro Phe Ile
    1205                1210                1215

Tyr Leu  Asn Asn Ser Ile Pro  Asn Leu Ser Asp Phe  Glu Ala Glu
    1220                1225                1230

Leu Ser  Leu Trp Phe Lys Asn  His Thr Ser Ile Ala  Pro Asn Leu
    1235                1240                1245
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Thr Phe  Asn Ser His Ile Asn  Ala Thr Phe Leu Asp  Leu Tyr Tyr
    1250                1255                1260

Glu Met  Asn Val Ile Gln Glu  Ser Ile Lys Ser Leu  Asn Ser Ser
    1265                1270                1275

Phe Ile  Asn Leu Lys Glu Ile  Gly Thr Tyr Glu Met  Tyr Val Lys
    1280                1285                1290

Trp Pro  Trp Tyr Ile Trp Leu  Leu Ile Val Ile Leu  Phe Ile Ile
    1295                1300                1305

Phe Leu  Met Ile Leu Phe Phe  Ile Cys Cys Cys Thr  Gly Cys Gly
    1310                1315                1320

Ser Ala  Cys Phe Ser Lys Cys  His Asn Cys Cys Asp  Glu Tyr Gly
    1325                1330                1335

Gly His  Asn Asp Phe Val Ile  Lys Ala Ser His Asp  Asp
    1340                1345                1350


<210> SEQ ID NO 32
<211> LENGTH: 526
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 32

Met Phe Ile Phe Leu Leu Phe Leu Thr Leu Thr Ser Gly Ser Asp Leu
1               5                   10                  15

Asp Arg Ala Leu Ser Gly Ile Ala Ala Glu Gln Asp Arg Asn Thr Arg
            20                  25                  30

Glu Val Phe Ala Gln Val Lys Gln Met Tyr Lys Thr Pro Thr Leu Lys
        35                  40                  45

Tyr Phe Gly Gly Phe Asn Phe Ser Gln Ile Leu Pro Asp Pro Leu Lys
    50                  55                  60

Pro Thr Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr
65                  70                  75                  80

Leu Ala Asp Ala Gly Phe Met Lys Gln Tyr Gly Glu Cys Leu Gly Asp
                85                  90                  95

Ile Asn Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr
            100                 105                 110

Val Leu Pro Pro Leu Leu Thr Asp Asp Met Ile Ala Ala Tyr Thr Ala
        115                 120                 125

Ala Leu Val Ser Gly Thr Ala Thr Ala Gly Trp Thr Phe Gly Ala Gly
    130                 135                 140

Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn
145                 150                 155                 160

Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn Gln Lys Gln Ile
                165                 170                 175

Ala Asn Gln Phe Asn Lys Ala Ile Ser Gln Ile Gln Glu Ser Leu Thr
            180                 185                 190

Thr Thr Ser Thr Ala Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn
        195                 200                 205

Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly
    210                 215                 220

Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg Leu Asp Lys Val
225                 230                 235                 240

Glu Ala Glu Val Gln Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser
                245                 250                 255
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Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg
            260                 265                 270

Ala Ser Ala Asn Leu Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly
        275                 280                 285

Gln Ser Lys Arg Val Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser
    290                 295                 300

Phe Pro Gln Ala Ala Pro His Gly Val Val Phe Leu His Val Thr Tyr
305                 310                 315                 320

Val Pro Ser Gln Glu Arg Asn Phe Thr Thr Ala Pro Ala Ile Cys His
                325                 330                 335

Glu Gly Lys Ala Tyr Phe Pro Arg Glu Gly Val Phe Val Phe Asn Gly
            340                 345                 350

Thr Ser Trp Phe Ile Thr Gln Arg Asn Phe Phe Ser Pro Gln Ile Ile
        355                 360                 365

Thr Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly
    370                 375                 380

Ile Ile Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser
385                 390                 395                 400

Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp
                405                 410                 415

Val Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile
            420                 425                 430

Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu
        435                 440                 445

Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys
    450                 455                 460

Trp Pro Trp Tyr Val Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile
465                 470                 475                 480

Val Met Val Thr Ile Leu Leu Cys Cys Met Thr Ser Cys Cys Ser Cys
                485                 490                 495

Leu Lys Gly Ala Cys Ser Cys Gly Ser Cys Cys Lys Phe Asp Glu Asp
            500                 505                 510

Asp Ser Glu Pro Val Leu Lys Gly Val Lys Leu His Tyr Thr
        515                 520                 525


<210> SEQ ID NO 33
<211> LENGTH: 588
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 33

Met Ile His Ser Val Phe Leu Leu Met Phe Leu Leu Thr Pro Thr Glu
1               5                   10                  15

Ser Asp Cys Lys Leu Pro Leu Gly Gln Ser Leu Cys Ala Leu Pro Asp
            20                  25                  30

Thr Pro Ser Thr Leu Thr Pro Arg Ser Val Arg Ser Val Pro Gly Glu
        35                  40                  45

Met Arg Leu Ala Ser Ile Ala Phe Asn His Pro Ile Gln Val Asp Gln
    50                  55                  60

Leu Asn Ser Ser Tyr Phe Lys Leu Ser Ile Pro Thr Asn Phe Ser Phe
65                  70                  75                  80

Gly Val Thr Gln Glu Tyr Ile Gln Thr Thr Ile Gln Lys Val Thr Val
                85                  90                  95
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Asp Cys Lys Gln Tyr Val Cys Asn Gly Phe Gln Lys Cys Glu Gln Leu
            100                 105                 110

Leu Arg Glu Tyr Gly Gln Phe Cys Ser Lys Ile Asn Gln Ala Leu His
        115                 120                 125

Gly Ala Asn Leu Arg Gln Asp Asp Ser Val Arg Asn Leu Phe Ala Ser
    130                 135                 140

Val Lys Ser Ser Gln Ser Ser Pro Ile Ile Pro Gly Phe Gly Gly Asp
145                 150                 155                 160

Phe Asn Leu Thr Leu Leu Glu Pro Val Ser Ile Ser Thr Gly Ser Arg
                165                 170                 175

Ser Ala Arg Ser Ala Ile Glu Asp Leu Leu Phe Asp Lys Val Thr Ile
            180                 185                 190

Ala Asp Pro Gly Tyr Met Gln Gly Tyr Asp Asp Cys Met Gln Gln Gly
        195                 200                 205

Pro Ala Ser Ala Arg Asp Leu Ile Cys Ala Gln Tyr Val Ala Gly Tyr
    210                 215                 220

Lys Val Leu Pro Pro Leu Met Asp Val Asn Met Glu Ala Ala Tyr Thr
225                 230                 235                 240

Ser Ser Leu Leu Gly Ser Ile Ala Gly Val Gly Trp Thr Ala Gly Leu
                245                 250                 255

Ser Ser Phe Ala Ala Ile Pro Phe Ala Gln Ser Ile Phe Tyr Arg Leu
            260                 265                 270

Asn Gly Val Gly Ile Thr Gln Gln Val Leu Ser Glu Asn Gln Lys Leu
        275                 280                 285

Ile Ala Asn Lys Phe Asn Gln Ala Leu Gly Ala Met Gln Thr Gly Phe
    290                 295                 300

Thr Thr Thr Asn Glu Ala Phe Gln Lys Val Gln Asp Ala Val Asn Asn
305                 310                 315                 320

Asn Ala Gln Ala Leu Ser Lys Leu Ala Ser Glu Leu Ser Asn Thr Phe
                325                 330                 335

Gly Ala Ile Ser Ala Ser Ile Gly Asp Ile Ile Gln Arg Leu Asp Val
            340                 345                 350

Leu Glu Gln Asp Ala Gln Ile Asp Arg Leu Ile Asn Gly Arg Leu Thr
        355                 360                 365

Thr Leu Asn Ala Phe Val Ala Gln Gln Leu Val Arg Ser Glu Ser Ala
    370                 375                 380

Ala Leu Ser Ala Gln Leu Ala Lys Asp Lys Val Asn Glu Cys Val Lys
385                 390                 395                 400

Ala Gln Ser Lys Arg Ser Gly Phe Cys Gly Gln Gly Thr His Ile Val
                405                 410                 415

Ser Phe Val Val Asn Ala Pro Asn Gly Leu Tyr Phe Met His Val Gly
            420                 425                 430

Tyr Tyr Pro Ser Asn His Ile Glu Val Val Ser Ala Tyr Gly Leu Cys
        435                 440                 445

Asp Ala Ala Asn Pro Thr Asn Cys Ile Ala Pro Val Asn Gly Tyr Phe
    450                 455                 460

Ile Lys Thr Asn Asn Thr Arg Ile Val Asp Glu Trp Ser Tyr Thr Gly
465                 470                 475                 480

Ser Ser Phe Tyr Ala Pro Glu Pro Ile Thr Ser Leu Asn Thr Lys Tyr
                485                 490                 495

Val Ala Pro Gln Val Thr Tyr Gln Asn Ile Ser Thr Asn Leu Pro Pro
            500                 505                 510
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```
Pro Leu Leu Gly Asn Ser Thr Gly Ile Asp Phe Gln Asp Glu Leu Asp
        515                 520                 525

Glu Phe Phe Lys Asn Val Ser Thr Ser Ile Pro Asn Phe Gly Ser Leu
    530                 535                 540

Thr Gln Ile Asn Thr Thr Leu Leu Asp Leu Thr Tyr Glu Met Leu Ser
545                 550                 555                 560

Leu Gln Gln Val Val Lys Ala Leu Asn Glu Ser Tyr Ile Asp Leu Lys
                565                 570                 575

Glu Leu Gly Asn Tyr Thr Tyr Tyr Asn Lys Trp Pro
            580                 585


<210> SEQ ID NO 34
<211> LENGTH: 526
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 34

Met Phe Ile Phe Leu Leu Phe Leu Thr Leu Thr Ser Gly Ser Asp Leu
1               5                   10                  15

Asp Arg Ala Leu Ser Gly Ile Ala Ala Glu Gln Asp Arg Asn Thr Arg
            20                  25                  30

Glu Val Phe Ala Gln Val Lys Gln Met Tyr Lys Thr Pro Thr Leu Lys
        35                  40                  45

Tyr Phe Gly Gly Phe Asn Phe Ser Gln Ile Leu Pro Asp Pro Leu Lys
    50                  55                  60

Pro Thr Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr
65                  70                  75                  80

Leu Ala Asp Ala Gly Phe Met Lys Gln Tyr Gly Glu Cys Leu Gly Asp
                85                  90                  95

Ile Asn Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr
            100                 105                 110

Val Leu Pro Pro Leu Leu Thr Asp Asp Met Ile Ala Ala Tyr Thr Ala
        115                 120                 125

Ala Leu Val Ser Gly Thr Ala Thr Ala Gly Trp Thr Phe Gly Ala Gly
    130                 135                 140

Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn
145                 150                 155                 160

Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn Gln Lys Gln Ile
                165                 170                 175

Ala Asn Gln Phe Asn Lys Ala Ile Ser Gln Ile Gln Glu Ser Leu Thr
            180                 185                 190

Thr Thr Ser Thr Ala Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn
        195                 200                 205

Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly
    210                 215                 220

Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg Leu Asp Lys Val
225                 230                 235                 240

Glu Ala Glu Val Gln Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser
                245                 250                 255

Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg
            260                 265                 270

Ala Ser Ala Asn Leu Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly
        275                 280                 285
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```
Gln Ser Lys Arg Val Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser
    290                 295                 300

Phe Pro Gln Ala Ala Pro His Gly Val Val Phe Leu His Val Thr Tyr
305                 310                 315                 320

Val Pro Ser Gln Glu Arg Asn Phe Thr Thr Ala Pro Ala Ile Cys His
                325                 330                 335

Glu Gly Lys Ala Tyr Phe Pro Arg Glu Gly Val Phe Val Phe Asn Gly
            340                 345                 350

Thr Ser Trp Phe Ile Thr Gln Arg Asn Phe Phe Ser Pro Gln Ile Ile
        355                 360                 365

Thr Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly
    370                 375                 380

Ile Ile Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser
385                 390                 395                 400

Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp
                405                 410                 415

Val Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile
            420                 425                 430

Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu
        435                 440                 445

Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys
    450                 455                 460

Trp Pro Trp Tyr Val Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile
465                 470                 475                 480

Val Met Val Thr Ile Leu Leu Cys Cys Met Thr Ser Cys Cys Ser Cys
                485                 490                 495

Leu Lys Gly Ala Cys Ser Cys Gly Ser Cys Cys Lys Phe Asp Glu Asp
            500                 505                 510

Asp Ser Glu Pro Val Leu Lys Gly Val Lys Leu His Tyr Thr
        515                 520                 525


<210> SEQ ID NO 35
<211> LENGTH: 1864
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 35

tcaagctttt ggaccctcgt acagaagcta atacgactca ctatagggaa ataagagaga     60

aaagaagagt aagaagaaat ataagagcca ccatgggtct caaggtgaac gtctctgccg    120

tattcatggc agtactgtta actctccaaa cacccgccgg tcaaattcat tggggcaatc    180

tctctaagat aggggtagta ggaataggaa gtgcaagcta caaagttatg actcgttcca    240

gccatcaatc attagtcata aaattaatgc ccaatataac tctcctcaat aactgcacga    300

gggtagagat tgcagaatac aggagactac taagaacagt tttggaacca attagggatg    360

cacttaatgc aatgacccag aacataaggc cggttcagag cgtagcttca agtaggagac    420

acaagagatt tgcgggagta gtcctggcag gtgcggccct aggtgttgcc acagctgctc    480

agataacagc cggcattgca cttcaccggt ccatgctgaa ctctcaggcc atcgacaatc    540

tgagagcgag cctggaaact actaatcagg caattgaggc aatcagacaa gcagggcagg    600

agatgatatt ggctgttcag ggtgtccaag actacatcaa taatgagctg ataccgtcta    660

tgaaccagct atcttgtgat ctaatcggtc agaagctcgg gctcaaattg cttagatact    720
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atacagaaat cctgtcatta tttggcccca gcctacggga ccccatatct gcggagatat 780

ctatccaggc tttgagttat gcacttggag gagatatcaa taaggtgtta gaaaagctcg 840

gatacagtgg aggcgattta ctaggcatct tagagagcag aggaataaag gctcggataa 900

ctcacgtcga cacagagtcc tacttcatag tcctcagtat agcctatccg acgctgtccg 960

agattaaggg ggtgattgtc caccggctag agggggtctc gtacaacata ggctctcaag 1020

agtggtatac cactgtgccc aagtatgttg caacccaagg gtaccttatc tcgaattttg 1080

atgagtcatc atgtactttc atgccagagg ggactgtgtg cagccaaaat gccttgtacc 1140

cgatgagtcc tctgctccaa gaatgcctcc gggggtccac caagtcctgt gctcgtacac 1200

tcgtatccgg gtcttttggg aaccggttca ttttatcaca agggaaccta atagccaatt 1260

gtgcatcaat tctttgtaag tgttacacaa caggtacgat tattaatcaa gaccctgaca 1320

agatcctaac atacattgct gccgatcgct gcccggtagt cgaggtgaac ggcgtgacca 1380

tccaagtcgg gagcaggagg tatccagacg ctgtgtactt gcacagaatt gacctcggtc 1440

ctcccatatc attggagagg ttggacgtag ggacaaatct ggggaatgca attgccaaat 1500

tggaggatgc caaggaattg ttggaatcat cggaccagat attgagaagt atgaaaggtt 1560

tatcgagcac tagcatagtc tacatcctga ttgcagtgtg tcttggaggg ttgataggga 1620

tccccacttt aatatgttgc tgcaggggggc gttgtaacaa aaagggagaa caagttggta 1680

tgtcaagacc aggcctaaag cctgacctta caggaacatc aaaatcctat gtaagatcgc 1740

tttgatgata ataggctgga gcctcggtgg ccaagcttct tgcccccttgg gcctcccccc 1800

agcccctcct ccccttcctg cacccgtacc cccgtggtct ttgaataaag tctgagtggg 1860

cggc 1864

<210> SEQ ID NO 36
<211> LENGTH: 1653
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 36

atgggtctca aggtgaacgt ctctgccgta ttcatggcag tactgttaac tctccaaaca 60

cccgccggtc aaattcattg gggcaatctc tctaagatag gggtagtagg aataggaagt 120

gcaagctaca aagttatgac tcgttccagc catcaatcat tagtcataaa attaatgccc 180

aatataactc tcctcaataa ctgcacgagg gtagagattg cagaatacag gagactacta 240

agaacagttt tggaaccaat tagggatgca cttaatgcaa tgacccagaa cataaggccg 300

gttcagagcg tagcttcaag taggagacac aagagatttg cgggagtagt cctggcaggt 360

gcggccctag gtgttgccac agctgctcag ataacagccg gcattgcact tcaccggtcc 420

atgctgaact ctcaggccat cgacaatctg agagcgagcc tggaaactac taatcaggca 480

attgaggcaa tcagacaagc agggcaggag atgatattgg ctgttcaggg tgtccaagac 540

tacatcaata atgagctgat accgtctatg aaccagctat cttgtgatct aatcggtcag 600

aagctcgggc tcaaattgct tagatactat acagaaatcc tgtcattatt tggccccagc 660

ctacgggacc ccatatctgc ggagatatct atccaggctt tgagttatgc acttggagga 720

gatatcaata aggtgttaga aaagctcgga tacagtggag gcgatttact aggcatctta 780

gagagcagag gaataaaggc tcggataact cacgtcgaca cagagtccta cttcatagtc 840

ctcagtatag cctatccgac gctgtccgag attaaggggg tgattgtcca ccggctagag 900

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ggggtctcgt acaacatagg ctctcaagag tggtatacca ctgtgcccaa gtatgttgca    960

acccaagggt accttatctc gaattttgat gagtcatcat gtactttcat gccagagggg   1020

actgtgtgca gccaaaatgc cttgtacccg atgagtcctc tgctccaaga atgcctccgg   1080

gggtccacca agtcctgtgc tcgtacactc gtatccgggt cttttgggaa ccggttcatt   1140

ttatcacaag ggaacctaat agccaattgt gcatcaattc tttgtaagtg ttacacaaca   1200

ggtacgatta ttaatcaaga ccctgacaag atcctaacat acattgctgc cgatcgctgc   1260

ccggtagtcg aggtgaacgg cgtgaccatc caagtcggga gcaggaggta tccagacgct   1320

gtgtacttgc acagaattga cctcggtcct cccatatcat tggagaggtt ggacgtaggg   1380

acaaatctgg ggaatgcaat tgccaaattg gaggatgcca aggaattgtt ggaatcatcg   1440

gaccagatat tgagaagtat gaaaggttta tcgagcacta gcatagtcta catcctgatt   1500

gcagtgtgtc ttggagggtt gatagggatc cccactttaa tatgttgctg caggggggcgt   1560

tgtaacaaaa agggagaaca agttggtatg tcaagaccag gcctaaagcc tgaccttaca   1620

ggaacatcaa aatcctatgt aagatcgctt tga                                1653


<210> SEQ ID NO 37
<211> LENGTH: 1925
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 37

ggggaaataa gagagaaaag aagagtaaga agaaatataa gagccaccat gggtctcaag     60

gtgaacgtct ctgccgtatt catggcagta ctgttaactc tccaaacacc cgccggtcaa    120

attcattggg gcaatctctc taagataggg gtagtaggaa taggaagtgc aagctacaaa    180

gttatgactc gttccagcca tcaatcatta gtcataaaat taatgcccaa tataactctc    240

ctcaataact gcacgagggt agagattgca gaatacagga gactactaag aacagttttg    300

gaaccaatta gggatgcact taatgcaatg acccagaaca taaggccggt tcagagcgta    360

gcttcaagta ggagacacaa gagatttgcg ggagtagtcc tggcaggtgc ggccctaggt    420

gttgccacag ctgctcagat aacagccggc attgcacttc accggtccat gctgaactct    480

caggccatcg acaatctgag agcgagcctg gaaactacta atcaggcaat tgaggcaatc    540

agacaagcag ggcaggagat gatattggct gttcagggtg tccaagacta catcaataat    600

gagctgatac cgtctatgaa ccagctatct tgtgatctaa tcggtcagaa gctcgggctc    660

aaattgctta gatactatac agaaatcctg tcattatttg gccccagcct acgggacccc    720

atatctgcgg agatatctat ccaggctttg agttatgcac ttggaggaga tatcaataag    780

gtgttagaaa agctcggata cagtggaggc gatttactag gcatcttaga gagcagagga    840

ataaaggctc ggataactca cgtcgacaca gagtcctact tcatagtcct cagtatagcc    900

tatccgacgc tgtccgagat taaggggtg attgtccacc ggctagaggg ggtctcgtac    960

aacataggct ctcaagagtg gtataccact gtgcccaagt atgttgcaac ccaagggtac   1020

cttatctcga attttgatga gtcatcatgt actttcatgc cagaggggac tgtgtgcagc   1080

caaaatgcct tgtacccgat gagtcctctg ctccaagaat gcctccgggg gtccaccaag   1140

tcctgtgctc gtacactcgt atccgggtct tttgggaacc ggttcatttt atcacaaggg   1200

aacctaatag ccaattgtgc atcaattctt tgtaagtgtt acacaacagg tacgattatt   1260
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aatcaagacc ctgacaagat cctaacatac attgctgccg atcgctgccc ggtagtcgag 1320

gtgaacggcg tgaccatcca agtcgggagc aggaggtatc cagacgctgt gtacttgcac 1380

agaattgacc tcggtcctcc catatcattg gagaggttgg acgtagggac aaatctgggg 1440

aatgcaattg ccaaattgga ggatgccaag gaattgttgg aatcatcgga ccagatattg 1500

agaagtatga aaggtttatc gagcactagc atagtctaca tcctgattgc agtgtgtctt 1560

ggagggttga tagggatccc cactttaata tgttgctgca gggggcgttg taacaaaaag 1620

ggagaacaag ttggtatgtc aagaccaggc ctaaagcctg accttacagg aacatcaaaa 1680

tcctatgtaa gatcgctttg atgataatag gctggagcct cggtggccaa gcttcttgcc 1740

ccttgggcct ccccccagcc cctcctcccc ttcctgcacc cgtacccccg tggtctttga 1800

ataaagtctg agtgggcggc aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1860

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1920

tctag 1925

<210> SEQ ID NO 38
<211> LENGTH: 1864
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 38

tcaagctttt ggaccctcgt acagaagcta atacgactca ctatagggaa ataagagaga 60

aaagaagagt aagaagaaat ataagagcca ccatgggtct caaggtgaac gtctctgtca 120

tattcatggc agtactgtta actcttcaaa cacccaccgg tcaaatccat tggggcaatc 180

tctctaagat aggggtggta ggggtaggaa gtgcaagcta caaagttatg actcgttcca 240

gccatcaatc attagtcata aagttaatgc ccaatataac tctcctcaac aattgcacga 300

gggtagggat tgcagaatac aggagactac tgagaacagt tctggaacca attagagatg 360

cacttaatgc aatgacccag aatataagac cggttcagag tgtagcttca agtaggagac 420

acaagagatt tgcgggagtt gtcctggcag gtgcggccct aggcgttgcc acagctgctc 480

aaataacagc cggtattgca cttcaccagt ccatgctgaa ctctcaagcc atcgacaatc 540

tgagagcgag cctagaaact actaatcagg caattgaggc aatcagacaa gcagggcagg 600

agatgatatt ggctgttcag ggtgtccaag actacatcaa taatgagctg ataccgtcta 660

tgaatcaact atcttgtgat ttaatcggcc agaagctagg gctcaaattg ctcagatact 720

atacagaaat cctgtcatta tttggcccca gcttacggga ccccatatct gcggagatat 780

ctatccaggc tttgagctat gcgcttggag gagatatcaa taaggtgttg gaaaagctcg 840

gatacagtgg aggtgatcta ctgggcatct tagagagcag aggaataaag gcccggataa 900

ctcacgtcga cacagagtcc tacttcattg tactcagtat agcctatccg acgctatccg 960

agattaaggg ggtgattgtc caccggctag agggggtctc gtacaacata ggctctcaag 1020

agtggtatac cactgtgccc aagtatgttg caacccaagg gtaccttatc tcgaattttg 1080

atgagtcatc atgcactttc atgccagagg ggactgtgtg cagccagaat gccttgtacc 1140

cgatgagtcc tctgctccaa gaatgcctcc gggggtccac taagtcctgt gctcgtacac 1200

tcgtatccgg gtctttcggg aaccggttca ttttatcaca ggggaaccta atagccaatt 1260

gtgcatcaat cctttgcaag tgttacacaa caggaacaat cattaatcaa gaccctgaca 1320

agatcctaac atacattgct gccgatcact gcccggtggt cgaggtgaat ggcgtgacca 1380

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tccaagtcgg gagcaggagg tatccggacg ctgtgtactt gcacaggatt gacctcggtc 1440

ctcccatatc tttggagagg ttggacgtag ggacaaatct ggggaatgca attgctaagt 1500

tggaggatgc caaggaattg ttggagtcat cggaccagat attgaggagt atgaaaggtt 1560

tatcgagcac tagtatagtt tacatcctga ttgcagtgtg tcttggagga ttgataggga 1620

tccccgcttt aatatgttgc tgcaggggggc gttgtaacaa gaagggagaa caagttggta 1680

tgtcaagacc aggcctaaag cctgatctta caggaacatc aaaatcctat gtaaggtcac 1740

tctgatgata ataggctgga gcctcggtgg ccaagcttct tgccccttgg gcctcccccc 1800

agcccctcct ccccttcctg cacccgtacc cccgtggtct ttgaataaag tctgagtggg 1860

cggc 1864

<210> SEQ ID NO 39
<211> LENGTH: 1653
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 39

atgggtctca aggtgaacgt ctctgtcata ttcatggcag tactgttaac tcttcaaaca 60

cccaccggtc aaatccattg gggcaatctc tctaagatag gggtggtagg ggtaggaagt 120

gcaagctaca aagttatgac tcgttccagc catcaatcat tagtcataaa gttaatgccc 180

aatataactc tcctcaacaa ttgcacgagg gtagggattg cagaatacag gagactactg 240

agaacagttc tggaaccaat tagagatgca cttaatgcaa tgacccagaa tataagaccg 300

gttcagagtg tagcttcaag taggagacac aagagatttg cgggagttgt cctggcaggt 360

gcggccctag gcgttgccac agctgctcaa ataacagccg gtattgcact tcaccagtcc 420

atgctgaact ctcaagccat cgacaatctg agagcgagcc tagaaactac taatcaggca 480

attgaggcaa tcagacaagc agggcaggag atgatattgg ctgttcaggg tgtccaagac 540

tacatcaata atgagctgat accgtctatg aatcaactat cttgtgattt aatcggccag 600

aagctagggc tcaaattgct cagatactat acagaaatcc tgtcattatt tggccccagc 660

ttacgggacc ccatatctgc ggagatatct atccaggctt tgagctatgc gcttggagga 720

gatatcaata aggtgttgga aaagctcgga tacagtggag gtgatctact gggcatctta 780

gagagcagag gaataaaggc ccggataact cacgtcgaca cagagtccta cttcattgta 840

ctcagtatag cctatccgac gctatccgag attaaggggg tgattgtcca ccggctagag 900

ggggtctcgt acaacatagg ctctcaagag tggtatacca ctgtgcccaa gtatgttgca 960

acccaagggt accttatctc gaattttgat gagtcatcat gcactttcat gccagagggg 1020

actgtgtgca gccagaatgc cttgtacccg atgagtcctc tgctccaaga atgcctccgg 1080

gggtccacta agtcctgtgc tcgtacactc gtatccgggt ctttcgggaa ccggttcatt 1140

ttatcacagg ggaacctaat agccaattgt gcatcaatcc tttgcaagtg ttacacaaca 1200

ggaacaatca ttaatcaaga ccctgacaag atcctaacat acattgctgc cgatcactgc 1260

ccggtggtcg aggtgaatgg cgtgaccatc caagtcggga gcaggaggta tccggacgct 1320

gtgtacttgc acaggattga cctcggtcct cccatatctt tggagaggtt ggacgtaggg 1380

acaaatctgg ggaatgcaat tgctaagttg gaggatgcca aggaattgtt ggagtcatcg 1440

gaccagatat tgaggagtat gaaaggttta tcgagcacta gtatagttta catcctgatt 1500

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gcagtgtgtc ttggaggatt gatagggatc cccgctttaa tatgttgctg caggggggcgt 1560

tgtaacaaga agggagaaca agttggtatg tcaagaccag gcctaaagcc tgatcttaca 1620

ggaacatcaa aatcctatgt aaggtcactc tga 1653

<210> SEQ ID NO 40
<211> LENGTH: 1925
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 40

ggggaaataa gagagaaaag aagagtaaga agaaatataa gagccaccat gggtctcaag 60

gtgaacgtct ctgtcatatt catggcagta ctgttaactc ttcaaacacc caccggtcaa 120

atccattggg gcaatctctc taagataggg gtggtagggg taggaagtgc aagctacaaa 180

gttatgactc gttccagcca tcaatcatta gtcataaagt taatgcccaa tataactctc 240

ctcaacaatt gcacgagggt agggattgca gaatacagga gactactgag aacagttctg 300

gaaccaatta gagatgcact taatgcaatg acccagaata taagaccggt tcagagtgta 360

gcttcaagta ggagacacaa gagatttgcg ggagttgtcc tggcaggtgc ggccctaggc 420

gttgccacag ctgctcaaat aacagccggt attgcacttc accagtccat gctgaactct 480

caagccatcg acaatctgag agcgagccta gaaactacta atcaggcaat tgaggcaatc 540

agacaagcag ggcaggagat gatattggct gttcagggtg tccaagacta catcaataat 600

gagctgatac cgtctatgaa tcaactatct tgtgatttaa tcggccagaa gctagggctc 660

aaattgctca gatactatac agaaatcctg tcattatttg gccccagctt acgggacccc 720

atatctgcgg agatatctat ccaggctttg agctatgcgc ttggaggaga tatcaataag 780

gtgttggaaa agctcggata cagtggaggt gatctactgg gcatcttaga gagcagagga 840

ataaaggccc ggataactca cgtcgacaca gagtcctact tcattgtact cagtatagcc 900

tatccgacgc tatccgagat taaggggtg attgtccacc ggctagaggg ggtctcgtac 960

aacataggct ctcaagagtg gtataccact gtgcccaagt atgttgcaac ccaagggtac 1020

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tcctgtgctc gtacactcgt atccgggtct ttcgggaacc ggttcatttt atcacagggg 1200

aacctaatag ccaattgtgc atcaatcctt tgcaagtgtt acacaacagg aacaatcatt 1260

aatcaagacc ctgacaagat cctaacatac attgctgccg atcactgccc ggtggtcgag 1320

gtgaatggcg tgaccatcca agtcgggagc aggaggtatc cggacgctgt gtacttgcac 1380

aggattgacc tcggtcctcc catatctttg gagaggttgg acgtagggac aaatctgggg 1440

aatgcaattg ctaagttgga ggatgccaag gaattgttgg agtcatcgga ccagatattg 1500

aggagtatga aaggtttatc gagcactagt atagtttaca tcctgattgc agtgtgtctt 1560

ggaggattga tagggatccc cgctttaata tgttgctgca gggggcgttg taacaagaag 1620

ggagaacaag ttggtatgtc aagaccaggc ctaaagcctg atcttacagg aacatcaaaa 1680

tcctatgtaa ggtcactctg atgataatag gctggagcct cggtggccaa gcttcttgcc 1740

ccttgggcct ccccccagcc cctcctcccc ttcctgcacc cgtacccccg tggtctttga 1800

ataaagtctg agtgggcggc aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1860

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1920

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tctag 1925

<210> SEQ ID NO 41
<211> LENGTH: 2065
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 41

tcaagctttt ggaccctcgt acagaagcta atacgactca ctatagggaa ataagagaga 60

aaagaagagt aagaagaaat ataagagcca ccatgtcacc gcaacgagac cggataaatg 120

ccttctacaa agataaccct tatcccaagg gaagtaggat agttattaac agagaacatc 180

ttatgattga cagaccctat gttctgctgg ctgttctgtt cgtcatgttt ctgagcttga 240

tcggattgct ggcaattgca ggcattagac ttcatcgggc agccatctac accgcggaga 300

tccataaaag cctcagtacc aatctggatg tgactaactc catcgagcat caggtcaagg 360

acgtgctgac accactcttt aaaatcatcg gggatgaagt gggcctgaga acacctcaga 420

gattcactga cctagtgaaa ttcatctcgg acaagattaa attccttaat ccggataggg 480

agtacgactt cagagatctc acttggtgca tcaacccgcc agagaggatc aaactagatt 540

atgatcaata ctgtgcagat gtggctgctg aagagctcat gaatgcattg gtgaactcaa 600

ctctactgga gaccagaaca accactcagt tcctagctgt ctcaaaggga aactgctcag 660

ggcccactac aatcagaggt caattctcaa acatgtcgct gtccttgttg gacttgtact 720

taggtcgagg ttacaatgtg tcatctatag tcactatgac atcccaggga atgtatgggg 780

gaacctacct agttgaaaag cctaatctga acagcaaagg gtcagagttg tcacaactga 840

gcatgtaccg agtgtttgaa gtaggtgtga tcagaaaccc gggtttgggg gctccggtgt 900

tccatatgac aaactatttt gagcaaccag tcagtaatgg tctcggcaac tgtatggtgg 960

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atcagggatc agggaaaggt gtcagcttcc agctcgtcaa gctgggtgtc tggaaatccc 1080

caaccgacat gcaatcctgg gtccccttat caacggatga tccagtggta gacaggcttt 1140

acctctcatc tcacagaggt gtcatcgctg acaatcaagc aaaatgggct gtcccgacaa 1200

cacgaacaga tgacaagttg cgaatggaga catgcttcca gcaggcgtgt aaaggtaaaa 1260

tccaagcact ctgcgagaat cccgagtggg taccattgaa ggataacagg attccttcat 1320

acggggtcct gtctgttgat ctgagtctga cggttgagct taaaatcaaa attgcttcgg 1380

gattcgggcc attgatcaca cacggctcag ggatggacct atacaaatcc aactgcaaca 1440

atgtgtattg gctgactatt ccgccaatga gaaatctagc cttaggcgta atcaacacat 1500

tggagtggat accgagattc aaggttagtc ccaacctctt cactgtccca attaaggaag 1560

caggcgaaga ctgccatgcc ccaacatacc tacctgcgga ggtggacggt gatgtcaaac 1620

tcagttccaa cctggtgatt ctacctggtc aagatctcca atatgttttg gcaacctacg 1680

atacctccag ggttgagcat gctgtggttt attacgttta cagcccaagc cgctcatttt 1740

cttacttttа tccttttagg ttgcctataa agggggtccc aatcgaacta caagtggaat 1800

gcttcacatg ggatcaaaaa ctctggtgcc gtcacttctg tgtgcttgcg gactcagaat 1860

ccggtggact tatcactcac tctgggatgg tgggcatggg agtcagctgc acagctaccc 1920

gggaagatgg aaccaatcgc agataatgat aataggctgg agcctcggtg gccaagcttc 1980

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ttgccccttg ggcctccccc cagcccctcc tccccttcct gcacccgtac ccccgtggtc 2040

tttgaataaa gtctgagtgg gcggc 2065

<210> SEQ ID NO 42
<211> LENGTH: 1854
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 42

atgtcaccgc aacgagaccg gataaatgcc ttctacaaag ataacccttа tcccaaggga 60

agtaggatag ttattaacag agaacatctt atgattgaca gaccctatgt tctgctggct 120

gttctgttcg tcatgtttct gagcttgatc ggattgctgg caattgcagg cattagactt 180

catcgggcag ccatctacac cgcggagatc cataaaagcc tcagtaccaa tctggatgtg 240

actaactcca tcgagcatca ggtcaaggac gtgctgacac cactctttaa aatcatcggg 300

gatgaagtgg gcctgagaac acctcagaga ttcactgacc tagtgaaatt catctcggac 360

aagattaaat tccttaatcc ggatagggag tacgacttca gagatctcac ttggtgcatc 420

aacccgccag agaggatcaa actagattat gatcaatact gtgcagatgt ggctgctgaa 480

gagctcatga atgcattggt gaactcaact ctactggaga ccagaacaac cactcagttc 540

ctagctgtct caaagggaaa ctgctcaggg cccactacaa tcagaggtca attctcaaac 600

atgtcgctgt ccttgttgga cttgtactta ggtcgaggtt acaatgtgtc atctatagtc 660

actatgacat cccagggaat gtatgggggа acctacctag ttgaaaagcc taatctgaac 720

agcaaagggt cagagttgtc acaactgagc atgtaccgag tgtttgaagt aggtgtgatc 780

agaaacccgg gtttgggggc tccggtgttc catatgacaa actattttga gcaaccagtc 840

agtaatggtc tcggcaactg tatggtggct ttgggggagc tcaaactcgc agccctttgt 900

cacggggacg attctatcat aattccctat cagggatcag ggaaaggtgt cagcttccag 960

ctcgtcaagc tgggtgtctg gaaatcccca accgacatgc aatcctgggt ccccttatca 1020

acggatgatc cagtggtaga caggctttac ctctcatctc acagaggtgt catcgctgac 1080

aatcaagcaa aatgggctgt cccgacaaca cgaacagatg acaagttgcg aatggagaca 1140

tgcttccagc aggcgtgtaa aggtaaaatc caagcactct gcgagaatcc cgagtgggta 1200

ccattgaagg ataacaggat tccttcatac ggggtcctgt ctgttgatct gagtctgacg 1260

gttgagctta aaatcaaaat tgcttcggga ttcgggccat tgatcacaca cggctcaggg 1320

atggacctat acaaatccaa ctgcaacaat gtgtattggc tgactattcc gccaatgaga 1380

aatctagcct taggcgtaat caacacattg gagtggatac cgagattcaa ggttagtccc 1440

aacctcttca ctgtcccaat taaggaagca ggcgaagact gccatgcccc aacataccta 1500

cctgcggagg tggacggtga tgtcaaactc agttccaacc tggtgattct acctggtcaa 1560

gatctccaat atgttttggc aacctacgat acctccaggg ttgagcatgc tgtggtttat 1620

tacgtttaca gcccaagccg ctcatttttct tacttttatc cttttaggtt gcctataaag 1680

ggggtcccaa tcgaactaca agtggaatgc ttcacatggg atcaaaaact ctggtgccgt 1740

cacttctgtg tgcttgcgga ctcagaatcc ggtggactta tcactcactc tgggatggtg 1800

ggcatgggag tcagctgcac agctacccgg gaagatggaa ccaatcgcag ataa 1854

<210> SEQ ID NO 43
<211> LENGTH: 2126

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 43

ggggaaataa gagagaaaag aagagtaaga agaaatataa gagccaccat gtcaccgcaa 60

cgagaccgga taaatgcctt ctacaaagat aacccttatc ccaagggaag taggatagtt 120

attaacagag aacatcttat gattgacaga ccctatgttc tgctggctgt tctgttcgtc 180

atgtttctga gcttgatcgg attgctggca attgcaggca ttagacttca tcgggcagcc 240

atctacaccg cggagatcca taaaagcctc agtaccaatc tggatgtgac taactccatc 300

gagcatcagg tcaaggacgt gctgacacca ctctttaaaa tcatcgggga tgaagtgggc 360

ctgagaacac ctcagagatt cactgaccta gtgaaattca tctcggacaa gattaaattc 420

cttaatccgg atagggagta cgacttcaga gatctcactt ggtgcatcaa cccgccagag 480

aggatcaaac tagattatga tcaatactgt gcagatgtgg ctgctgaaga gctcatgaat 540

gcattggtga actcaactct actggagacc agaacaacca ctcagttcct agctgtctca 600

aagggaaact gctcagggcc cactacaatc agaggtcaat tctcaaacat gtcgctgtcc 660

ttgttggact tgtacttagg tcgaggttac aatgtgtcat ctatagtcac tatgacatcc 720

cagggaatgt atgggggaac ctacctagtt gaaaagccta atctgaacag caaagggtca 780

gagttgtcac aactgagcat gtaccgagtg tttgaagtag gtgtgatcag aaacccgggt 840

ttgggggctc cggtgttcca tatgacaaac tattttgagc aaccagtcag taatggtctc 900

ggcaactgta tggtggcttt gggggagctc aaactcgcag ccctttgtca cggggacgat 960

tctatcataa ttccctatca gggatcaggg aaaggtgtca gcttccagct cgtcaagctg 1020

ggtgtctgga aatccccaac cgacatgcaa tcctgggtcc ccttatcaac ggatgatcca 1080

gtggtagaca ggctttacct ctcatctcac agaggtgtca tcgctgacaa tcaagcaaaa 1140

tgggctgtcc cgacaacacg aacagatgac aagttgcgaa tggagacatg cttccagcag 1200

gcgtgtaaag gtaaaatcca agcactctgc gagaatcccg agtgggtacc attgaaggat 1260

aacaggattc cttcatacgg ggtcctgtct gttgatctga gtctgacggt tgagcttaaa 1320

atcaaaattg cttcgggatt cgggccattg atcacacacg gctcagggat ggacctatac 1380

aaatccaact gcaacaatgt gtattggctg actattccgc caatgagaaa tctagcctta 1440

ggcgtaatca acacattgga gtggataccg agattcaagg ttagtcccaa cctcttcact 1500

gtcccaatta aggaagcagg cgaagactgc catgccccaa catacctacc tgcggaggtg 1560

gacggtgatg tcaaactcag ttccaacctg gtgattctac ctggtcaaga tctccaatat 1620

gttttggcaa cctacgatac ctccagggtt gagcatgctg tggtttatta cgtttacagc 1680

ccaagccgct cattttctta cttttatcct tttaggttgc ctataaaggg ggtcccaatc 1740

gaactacaag tggaatgctt cacatgggat caaaaactct ggtgccgtca cttctgtgtg 1800

cttgcggact cagaatccgg tggacttatc actcactctg ggatggtggg catgggagtc 1860

agctgcacag ctacccggga agatggaacc aatcgcagat aatgataata ggctggagcc 1920

tcggtggcca agcttcttgc cccttgggcc tccccccagc ccctcctccc cttcctgcac 1980

ccgtaccccc gtggtctttg aataaagtct gagtgggcgg caaaaaaaaa aaaaaaaaaa 2040

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2100

aaaaaaaaaa aaaaaaaaaa atctag 2126

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<210> SEQ ID NO 44
<211> LENGTH: 2065
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 44

tcaagctttt ggaccctcgt acagaagcta atacgactca ctatagggaa ataagagaga 60

aaagaagagt aagaagaaat ataagagcca ccatgtcacc acaacgagac cggataaatg 120

ccttctacaa agacaacccc catcctaagg gaagtaggat agttattaac agagaacatc 180

ttatgattga tagaccttat gttttgctgg ctgttctatt cgtcatgttt ctgagcttga 240

tcgggttgct agccattgca ggcattagac ttcatcgggc agccatctac accgcagaga 300

tccataaaag cctcagcacc aatctggatg taactaactc aatcgagcat caggttaagg 360

acgtgctgac accactcttc aagatcatcg gtgatgaagt gggcttgagg acacctcaga 420

gattcactga cctagtgaag ttcatctctg acaagattaa attccttaat ccggacaggg 480

aatacgactt cagagatctc acttggtgta tcaacccgcc agagagaatc aaattggatt 540

atgatcaata ctgtgcagat gtggctgctg aagaactcat gaatgcattg gtgaactcaa 600

ctctactgga gaccagggca accaatcagt tcctagctgt ctcaaaggga aactgctcag 660

ggcccactac aatcagaggc caattctcaa acatgtcgct gtccctgttg gacttgtatt 720

taagtcgagg ttacaatgtg tcatctatag tcactatgac atcccaggga atgtacgggg 780

gaacttacct agtggaaaag cctaatctga gcagcaaagg gtcagagttg tcacaactga 840

gcatgcaccg agtgtttgaa gtaggtgtta tcagaaatcc gggtttgggg gctccggtat 900

tccatatgac aaactatctt gagcaaccag tcagtaatga tttcagcaac tgcatggtgg 960

ctttgggggga gctcaagttc gcagccctct gtcacaggga agattctatc acaattccct 1020

atcagggatc agggaaaggt gtcagcttcc agcttgtcaa gctaggtgtc tggaaatccc 1080

caaccgacat gcaatcctgg gtccccctat caacggatga tccagtgata gacaggcttt 1140

acctctcatc tcacagaggc gttatcgctg acaatcaagc aaaatgggct gtcccgacaa 1200

cacggacaga tgacaagttg cgaatggaga catgcttcca gcaggcgtgt aagggtaaaa 1260

tccaagcact ttgcgagaat cccgagtgga caccattgaa ggataacagg attccttcat 1320

acggggtctt gtctgttgat ctgagtctga cagttgagct taaaatcaaa attgtttcag 1380

gattcgggcc attgatcaca cacggttcag ggatggacct atacaaatcc aaccacaaca 1440

atatgtattg gctgactatc ccgccaatga agaacctggc cttaggtgta atcaacacat 1500

tggagtggat accgagattc aaggttagtc ccaacctctt cactgttcca attaaggaag 1560

caggcgagga ctgccatgcc ccaacatacc tacctgcgga ggtggatggt gatgtcaaac 1620

tcagttccaa tctggtgatt ctacctggtc aagatctcca atatgttctg gcaacctacg 1680

atacttccag agttgaacat gctgtagttt attacgttta cagcccaagc cgctcatttt 1740

cttacttttа tccttttagg ttgcctgtaa ggggggtccc cattgaatta caagtggaat 1800

gcttcacatg ggaccaaaaa ctctggtgcc gtcacttctg tgtgcttgcg gactcagaat 1860

ctggtggaca tatcactcac tctgggatgg tgggcatggg agtcagctgc acagccactc 1920

gggaagatgg aaccagccgc agatagtgat aataggctgg agcctcggtg gccaagcttc 1980

ttgccccttg ggcctccccc cagcccctcc tccccttcct gcacccgtac ccccgtggtc 2040

tttgaataaa gtctgagtgg gcggc 2065

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<210> SEQ ID NO 45
<211> LENGTH: 1854
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 45

atgtcaccac aacgagaccg gataaatgcc ttctacaaag acaaccccca tcctaaggga 60

agtaggatag ttattaacag agaacatctt atgattgata gaccttatgt tttgctggct 120

gttctattcg tcatgtttct gagcttgatc gggttgctag ccattgcagg cattagactt 180

catcgggcag ccatctacac cgcagagatc cataaaagcc tcagcaccaa tctggatgta 240

actaactcaa tcgagcatca ggttaaggac gtgctgacac cactcttcaa gatcatcggt 300

gatgaagtgg gcttgaggac acctcagaga ttcactgacc tagtgaagtt catctctgac 360

aagattaaat tccttaatcc ggacagggaa tacgacttca gagatctcac ttggtgtatc 420

aacccgccag agagaatcaa attggattat gatcaatact gtgcagatgt ggctgctgaa 480

gaactcatga atgcattggt gaactcaact ctactggaga ccagggcaac caatcagttc 540

ctagctgtct caaagggaaa ctgctcaggg cccactacaa tcagaggcca attctcaaac 600

atgtcgctgt ccctgttgga cttgtattta agtcgaggtt acaatgtgtc atctatagtc 660

actatgacat cccagggaat gtacgggggа acttacctag tggaaaagcc taatctgagc 720

agcaaagggt cagagttgtc acaactgagc atgcaccgag tgtttgaagt aggtgttatc 780

agaaatccgg gtttgggggc tccggtattc catatgacaa actatcttga gcaaccagtc 840

agtaatgatt tcagcaactg catggtggct ttgggggagc tcaagttcgc agccctctgt 900

cacagggaag attctatcac aattccctat cagggatcag ggaaaggtgt cagcttccag 960

cttgtcaagc taggtgtctg gaaatcccca accgacatgc aatcctgggt ccccctatca 1020

acggatgatc cagtgataga caggctttac ctctcatctc acagaggcgt tatcgctgac 1080

aatcaagcaa aatgggctgt cccgacaaca cggacagatg acaagttgcg aatggagaca 1140

tgcttccagc aggcgtgtaa gggtaaaatc caagcacttt gcgagaatcc cgagtggaca 1200

ccattgaagg ataacaggat tccttcatac ggggtcttgt ctgttgatct gagtctgaca 1260

gttgagctta aaatcaaaat tgtttcagga ttcgggccat tgatcacaca cggttcaggg 1320

atggacctat acaaatccaa ccacaacaat atgtattggc tgactatccc gccaatgaag 1380

aacctggcct taggtgtaat caacacattg gagtggatac cgagattcaa ggttagtccc 1440

aacctcttca ctgttccaat taaggaagca ggcgaggact gccatgcccc aacataccta 1500

cctgcggagg tggatggtga tgtcaaactc agttccaatc tggtgattct acctggtcaa 1560

gatctccaat atgttctggc aacctacgat acttccagag ttgaacatgc tgtagtttat 1620

tacgtttaca gcccaagccg ctcatttttct tacttttatc cttttaggtt gcctgtaagg 1680

ggggtcccca ttgaattaca agtggaatgc ttcacatggg accaaaaact ctggtgccgt 1740

cacttctgtg tgcttgcgga ctcagaatct ggtggacata tcactcactc tgggatggtg 1800

ggcatgggag tcagctgcac agccactcgg gaagatggaa ccagccgcag atag 1854

<210> SEQ ID NO 46
<211> LENGTH: 2126
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 46

ggggaaataa gagagaaaag aagagtaaga agaaatataa gagccaccat gtcaccacaa 60

cgagaccgga taaatgcctt ctacaaagac aacccccatc ctaagggaag taggatagtt 120

attaacagag aacatcttat gattgataga ccttatgttt tgctggctgt tctattcgtc 180

atgtttctga gcttgatcgg gttgctagcc attgcaggca ttagacttca tcgggcagcc 240

atctacaccg cagagatcca taaaagcctc agcaccaatc tggatgtaac taactcaatc 300

gagcatcagg ttaaggacgt gctgacacca ctcttcaaga tcatcggtga tgaagtgggc 360

ttgaggacac ctcagagatt cactgaccta gtgaagttca tctctgacaa gattaaattc 420

cttaatccgg acagggaata cgacttcaga gatctcactt ggtgtatcaa cccgccagag 480

agaatcaaat tggattatga tcaatactgt gcagatgtgg ctgctgaaga actcatgaat 540

gcattggtga actcaactct actggagacc agggcaacca atcagttcct agctgtctca 600

aagggaaact gctcagggcc cactacaatc agaggccaat tctcaaacat gtcgctgtcc 660

ctgttggact tgtatttaag tcgaggttac aatgtgtcat ctatagtcac tatgacatcc 720

cagggaatgt acgggggaac ttacctagtg gaaaagccta atctgagcag caaagggtca 780

gagttgtcac aactgagcat gcaccgagtg tttgaagtag gtgttatcag aaatccgggt 840

ttgggggctc cggtattcca tatgacaaac tatcttgagc aaccagtcag taatgatttc 900

agcaactgca tggtggcttt gggggagctc aagttcgcag ccctctgtca cagggaagat 960

tctatcacaa ttccctatca gggatcaggg aaaggtgtca gcttccagct tgtcaagcta 1020

ggtgtctgga aatccccaac cgacatgcaa tcctgggtcc ccctatcaac ggatgatcca 1080

gtgatagaca ggctttacct ctcatctcac agaggcgtta tcgctgacaa tcaagcaaaa 1140

tgggctgtcc cgacaacacg gacagatgac aagttgcgaa tggagacatg cttccagcag 1200

gcgtgtaagg gtaaaatcca agcactttgc gagaatcccg agtggacacc attgaaggat 1260

aacaggattc cttcatacgg ggtcttgtct gttgatctga gtctgacagt tgagcttaaa 1320

atcaaaattg tttcaggatt cgggccattg atcacacacg gttcagggat ggacctatac 1380

aaatccaacc acaacaatat gtattggctg actatcccgc caatgaagaa cctggcctta 1440

ggtgtaatca acacattgga gtggataccg agattcaagg ttagtcccaa cctcttcact 1500

gttccaatta aggaagcagg cgaggactgc catgccccaa catacctacc tgcggaggtg 1560

gatggtgatg tcaaactcag ttccaatctg gtgattctac ctggtcaaga tctccaatat 1620

gttctggcaa cctacgatac ttccagagtt gaacatgctg tagtttatta cgtttacagc 1680

ccaagccgct cattttctta cttttatcct tttaggttgc ctgtaagggg ggtccccatt 1740

gaattacaag tggaatgctt cacatgggac caaaaactct ggtgccgtca cttctgtgtg 1800

cttgcggact cagaatctgg tggacatatc actcactctg ggatggtggg catgggagtc 1860

agctgcacag ccactcggga agatggaacc agccgcagat agtgataata ggctggagcc 1920

tcggtggcca agcttcttgc cccttgggcc tccccccagc ccctcctccc cttcctgcac 1980

ccgtaccccc gtggtctttg aataaagtct gagtgggcgg caaaaaaaaa aaaaaaaaaa 2040

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2100

aaaaaaaaaa aaaaaaaaaa atctag 2126

<210> SEQ ID NO 47
<211> LENGTH: 550

<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 47

```
Met Gly Leu Lys Val Asn Val Ser Ala Val Phe Met Ala Val Leu Leu
1               5                  10                  15

Thr Leu Gln Thr Pro Ala Gly Gln Ile His Trp Gly Asn Leu Ser Lys
            20                  25                  30

Ile Gly Val Val Gly Ile Gly Ser Ala Ser Tyr Lys Val Met Thr Arg
        35                  40                  45

Ser Ser His Gln Ser Leu Val Ile Lys Leu Met Pro Asn Ile Thr Leu
    50                  55                  60

Leu Asn Asn Cys Thr Arg Val Glu Ile Ala Glu Tyr Arg Arg Leu Leu
65                  70                  75                  80

Arg Thr Val Leu Glu Pro Ile Arg Asp Ala Leu Asn Ala Met Thr Gln
                85                  90                  95

Asn Ile Arg Pro Val Gln Ser Val Ala Ser Ser Arg Arg His Lys Arg
            100                 105                 110

Phe Ala Gly Val Val Leu Ala Gly Ala Ala Leu Gly Val Ala Thr Ala
        115                 120                 125

Ala Gln Ile Thr Ala Gly Ile Ala Leu His Arg Ser Met Leu Asn Ser
    130                 135                 140

Gln Ala Ile Asp Asn Leu Arg Ala Ser Leu Glu Thr Thr Asn Gln Ala
145                 150                 155                 160

Ile Glu Ala Ile Arg Gln Ala Gly Gln Glu Met Ile Leu Ala Val Gln
                165                 170                 175

Gly Val Gln Asp Tyr Ile Asn Asn Glu Leu Ile Pro Ser Met Asn Gln
            180                 185                 190

Leu Ser Cys Asp Leu Ile Gly Gln Lys Leu Gly Leu Lys Leu Leu Arg
        195                 200                 205

Tyr Tyr Thr Glu Ile Leu Ser Leu Phe Gly Pro Ser Leu Arg Asp Pro
    210                 215                 220

Ile Ser Ala Glu Ile Ser Ile Gln Ala Leu Ser Tyr Ala Leu Gly Gly
225                 230                 235                 240

Asp Ile Asn Lys Val Leu Glu Lys Leu Gly Tyr Ser Gly Gly Asp Leu
                245                 250                 255

Leu Gly Ile Leu Glu Ser Arg Gly Ile Lys Ala Arg Ile Thr His Val
            260                 265                 270

Asp Thr Glu Ser Tyr Phe Ile Val Leu Ser Ile Ala Tyr Pro Thr Leu
        275                 280                 285

Ser Glu Ile Lys Gly Val Ile Val His Arg Leu Glu Gly Val Ser Tyr
    290                 295                 300

Asn Ile Gly Ser Gln Glu Trp Tyr Thr Thr Val Pro Lys Tyr Val Ala
305                 310                 315                 320

Thr Gln Gly Tyr Leu Ile Ser Asn Phe Asp Glu Ser Ser Cys Thr Phe
                325                 330                 335

Met Pro Glu Gly Thr Val Cys Ser Gln Asn Ala Leu Tyr Pro Met Ser
            340                 345                 350

Pro Leu Leu Gln Glu Cys Leu Arg Gly Ser Thr Lys Ser Cys Ala Arg
        355                 360                 365

Thr Leu Val Ser Gly Ser Phe Gly Asn Arg Phe Ile Leu Ser Gln Gly
    370                 375                 380
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Asn Leu Ile Ala Asn Cys Ala Ser Ile Leu Cys Lys Cys Tyr Thr Thr
385                 390                 395                 400

Gly Thr Ile Ile Asn Gln Asp Pro Asp Lys Ile Leu Thr Tyr Ile Ala
                405                 410                 415

Ala Asp Arg Cys Pro Val Val Glu Val Asn Gly Val Thr Ile Gln Val
            420                 425                 430

Gly Ser Arg Arg Tyr Pro Asp Ala Val Tyr Leu His Arg Ile Asp Leu
        435                 440                 445

Gly Pro Pro Ile Ser Leu Glu Arg Leu Asp Val Gly Thr Asn Leu Gly
    450                 455                 460

Asn Ala Ile Ala Lys Leu Glu Asp Ala Lys Glu Leu Leu Glu Ser Ser
465                 470                 475                 480

Asp Gln Ile Leu Arg Ser Met Lys Gly Leu Ser Ser Thr Ser Ile Val
                485                 490                 495

Tyr Ile Leu Ile Ala Val Cys Leu Gly Gly Leu Ile Gly Ile Pro Thr
            500                 505                 510

Leu Ile Cys Cys Cys Arg Gly Arg Cys Asn Lys Lys Gly Glu Gln Val
        515                 520                 525

Gly Met Ser Arg Pro Gly Leu Lys Pro Asp Leu Thr Gly Thr Ser Lys
    530                 535                 540

Ser Tyr Val Arg Ser Leu
545                 550


<210> SEQ ID NO 48
<211> LENGTH: 550
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 48

Met Gly Leu Lys Val Asn Val Ser Val Ile Phe Met Ala Val Leu Leu
1               5                   10                  15

Thr Leu Gln Thr Pro Thr Gly Gln Ile His Trp Gly Asn Leu Ser Lys
            20                  25                  30

Ile Gly Val Val Gly Val Gly Ser Ala Ser Tyr Lys Val Met Thr Arg
        35                  40                  45

Ser Ser His Gln Ser Leu Val Ile Lys Leu Met Pro Asn Ile Thr Leu
    50                  55                  60

Leu Asn Asn Cys Thr Arg Val Gly Ile Ala Glu Tyr Arg Arg Leu Leu
65                  70                  75                  80

Arg Thr Val Leu Glu Pro Ile Arg Asp Ala Leu Asn Ala Met Thr Gln
                85                  90                  95

Asn Ile Arg Pro Val Gln Ser Val Ala Ser Ser Arg Arg His Lys Arg
            100                 105                 110

Phe Ala Gly Val Val Leu Ala Gly Ala Ala Leu Gly Val Ala Thr Ala
        115                 120                 125

Ala Gln Ile Thr Ala Gly Ile Ala Leu His Gln Ser Met Leu Asn Ser
    130                 135                 140

Gln Ala Ile Asp Asn Leu Arg Ala Ser Leu Glu Thr Thr Asn Gln Ala
145                 150                 155                 160

Ile Glu Ala Ile Arg Gln Ala Gly Gln Glu Met Ile Leu Ala Val Gln
                165                 170                 175

Gly Val Gln Asp Tyr Ile Asn Asn Glu Leu Ile Pro Ser Met Asn Gln
            180                 185                 190
```

```
Leu Ser Cys Asp Leu Ile Gly Gln Lys Leu Gly Leu Lys Leu Leu Arg
        195                 200                 205

Tyr Tyr Thr Glu Ile Leu Ser Leu Phe Gly Pro Ser Leu Arg Asp Pro
    210                 215                 220

Ile Ser Ala Glu Ile Ser Ile Gln Ala Leu Ser Tyr Ala Leu Gly Gly
225                 230                 235                 240

Asp Ile Asn Lys Val Leu Glu Lys Leu Gly Tyr Ser Gly Gly Asp Leu
                245                 250                 255

Leu Gly Ile Leu Glu Ser Arg Gly Ile Lys Ala Arg Ile Thr His Val
            260                 265                 270

Asp Thr Glu Ser Tyr Phe Ile Val Leu Ser Ile Ala Tyr Pro Thr Leu
        275                 280                 285

Ser Glu Ile Lys Gly Val Ile Val His Arg Leu Glu Gly Val Ser Tyr
    290                 295                 300

Asn Ile Gly Ser Gln Glu Trp Tyr Thr Thr Val Pro Lys Tyr Val Ala
305                 310                 315                 320

Thr Gln Gly Tyr Leu Ile Ser Asn Phe Asp Glu Ser Ser Cys Thr Phe
                325                 330                 335

Met Pro Glu Gly Thr Val Cys Ser Gln Asn Ala Leu Tyr Pro Met Ser
            340                 345                 350

Pro Leu Leu Gln Glu Cys Leu Arg Gly Ser Thr Lys Ser Cys Ala Arg
        355                 360                 365

Thr Leu Val Ser Gly Ser Phe Gly Asn Arg Phe Ile Leu Ser Gln Gly
    370                 375                 380

Asn Leu Ile Ala Asn Cys Ala Ser Ile Leu Cys Lys Cys Tyr Thr Thr
385                 390                 395                 400

Gly Thr Ile Ile Asn Gln Asp Pro Asp Lys Ile Leu Thr Tyr Ile Ala
                405                 410                 415

Ala Asp His Cys Pro Val Val Glu Val Asn Gly Val Thr Ile Gln Val
            420                 425                 430

Gly Ser Arg Arg Tyr Pro Asp Ala Val Tyr Leu His Arg Ile Asp Leu
        435                 440                 445

Gly Pro Pro Ile Ser Leu Glu Arg Leu Asp Val Gly Thr Asn Leu Gly
    450                 455                 460

Asn Ala Ile Ala Lys Leu Glu Asp Ala Lys Glu Leu Leu Glu Ser Ser
465                 470                 475                 480

Asp Gln Ile Leu Arg Ser Met Lys Gly Leu Ser Ser Thr Ser Ile Val
                485                 490                 495

Tyr Ile Leu Ile Ala Val Cys Leu Gly Gly Leu Ile Gly Ile Pro Ala
            500                 505                 510

Leu Ile Cys Cys Cys Arg Gly Arg Cys Asn Lys Lys Gly Glu Gln Val
        515                 520                 525

Gly Met Ser Arg Pro Gly Leu Lys Pro Asp Leu Thr Gly Thr Ser Lys
    530                 535                 540

Ser Tyr Val Arg Ser Leu
545                 550


<210> SEQ ID NO 49
<211> LENGTH: 617
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 49
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Met Ser Pro Gln Arg Asp Arg Ile Asn Ala Phe Tyr Lys Asp Asn Pro
1               5                  10                  15

Tyr Pro Lys Gly Ser Arg Ile Val Ile Asn Arg Glu His Leu Met Ile
            20                  25                  30

Asp Arg Pro Tyr Val Leu Leu Ala Val Leu Phe Val Met Phe Leu Ser
        35                  40                  45

Leu Ile Gly Leu Leu Ala Ile Ala Gly Ile Arg Leu His Arg Ala Ala
    50                  55                  60

Ile Tyr Thr Ala Glu Ile His Lys Ser Leu Ser Thr Asn Leu Asp Val
65                  70                  75                  80

Thr Asn Ser Ile Glu His Gln Val Lys Asp Val Leu Thr Pro Leu Phe
                85                  90                  95

Lys Ile Ile Gly Asp Glu Val Gly Leu Arg Thr Pro Gln Arg Phe Thr
            100                 105                 110

Asp Leu Val Lys Phe Ile Ser Asp Lys Ile Lys Phe Leu Asn Pro Asp
        115                 120                 125

Arg Glu Tyr Asp Phe Arg Asp Leu Thr Trp Cys Ile Asn Pro Pro Glu
    130                 135                 140

Arg Ile Lys Leu Asp Tyr Asp Gln Tyr Cys Ala Asp Val Ala Ala Glu
145                 150                 155                 160

Glu Leu Met Asn Ala Leu Val Asn Ser Thr Leu Leu Glu Thr Arg Thr
                165                 170                 175

Thr Thr Gln Phe Leu Ala Val Ser Lys Gly Asn Cys Ser Gly Pro Thr
            180                 185                 190

Thr Ile Arg Gly Gln Phe Ser Asn Met Ser Leu Ser Leu Leu Asp Leu
        195                 200                 205

Tyr Leu Gly Arg Gly Tyr Asn Val Ser Ser Ile Val Thr Met Thr Ser
    210                 215                 220

Gln Gly Met Tyr Gly Gly Thr Tyr Leu Val Glu Lys Pro Asn Leu Asn
225                 230                 235                 240

Ser Lys Gly Ser Glu Leu Ser Gln Leu Ser Met Tyr Arg Val Phe Glu
                245                 250                 255

Val Gly Val Ile Arg Asn Pro Gly Leu Gly Ala Pro Val Phe His Met
            260                 265                 270

Thr Asn Tyr Phe Glu Gln Pro Val Ser Asn Gly Leu Gly Asn Cys Met
        275                 280                 285

Val Ala Leu Gly Glu Leu Lys Leu Ala Ala Leu Cys His Gly Asp Asp
    290                 295                 300

Ser Ile Ile Ile Pro Tyr Gln Gly Ser Gly Lys Gly Val Ser Phe Gln
305                 310                 315                 320

Leu Val Lys Leu Gly Val Trp Lys Ser Pro Thr Asp Met Gln Ser Trp
                325                 330                 335

Val Pro Leu Ser Thr Asp Asp Pro Val Val Asp Arg Leu Tyr Leu Ser
            340                 345                 350

Ser His Arg Gly Val Ile Ala Asp Asn Gln Ala Lys Trp Ala Val Pro
        355                 360                 365

Thr Thr Arg Thr Asp Asp Lys Leu Arg Met Glu Thr Cys Phe Gln Gln
    370                 375                 380

Ala Cys Lys Gly Lys Ile Gln Ala Leu Cys Glu Asn Pro Glu Trp Val
385                 390                 395                 400

Pro Leu Lys Asp Asn Arg Ile Pro Ser Tyr Gly Val Leu Ser Val Asp
                405                 410                 415

Leu Ser Leu Thr Val Glu Leu Lys Ile Lys Ile Ala Ser Gly Phe Gly
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            420                 425                 430

Pro Leu Ile Thr His Gly Ser Gly Met Asp Leu Tyr Lys Ser Asn Cys
        435                 440                 445

Asn Asn Val Tyr Trp Leu Thr Ile Pro Pro Met Arg Asn Leu Ala Leu
    450                 455                 460

Gly Val Ile Asn Thr Leu Glu Trp Ile Pro Arg Phe Lys Val Ser Pro
465                 470                 475                 480

Asn Leu Phe Thr Val Pro Ile Lys Glu Ala Gly Glu Asp Cys His Ala
                485                 490                 495

Pro Thr Tyr Leu Pro Ala Glu Val Asp Gly Asp Val Lys Leu Ser Ser
            500                 505                 510

Asn Leu Val Ile Leu Pro Gly Gln Asp Leu Gln Tyr Val Leu Ala Thr
        515                 520                 525

Tyr Asp Thr Ser Arg Val Glu His Ala Val Val Tyr Tyr Val Tyr Ser
    530                 535                 540

Pro Ser Arg Ser Phe Ser Tyr Phe Tyr Pro Phe Arg Leu Pro Ile Lys
545                 550                 555                 560

Gly Val Pro Ile Glu Leu Gln Val Glu Cys Phe Thr Trp Asp Gln Lys
                565                 570                 575

Leu Trp Cys Arg His Phe Cys Val Leu Ala Asp Ser Glu Ser Gly Gly
            580                 585                 590

Leu Ile Thr His Ser Gly Met Val Gly Met Gly Val Ser Cys Thr Ala
        595                 600                 605

Thr Arg Glu Asp Gly Thr Asn Arg Arg
    610                 615


<210> SEQ ID NO 50
<211> LENGTH: 617
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 50

Met Ser Pro Gln Arg Asp Arg Ile Asn Ala Phe Tyr Lys Asp Asn Pro
1               5                   10                  15

His Pro Lys Gly Ser Arg Ile Val Ile Asn Arg Glu His Leu Met Ile
            20                  25                  30

Asp Arg Pro Tyr Val Leu Leu Ala Val Leu Phe Val Met Phe Leu Ser
        35                  40                  45

Leu Ile Gly Leu Leu Ala Ile Ala Gly Ile Arg Leu His Arg Ala Ala
    50                  55                  60

Ile Tyr Thr Ala Glu Ile His Lys Ser Leu Ser Thr Asn Leu Asp Val
65                  70                  75                  80

Thr Asn Ser Ile Glu His Gln Val Lys Asp Val Leu Thr Pro Leu Phe
                85                  90                  95

Lys Ile Ile Gly Asp Glu Val Gly Leu Arg Thr Pro Gln Arg Phe Thr
            100                 105                 110

Asp Leu Val Lys Phe Ile Ser Asp Lys Ile Lys Phe Leu Asn Pro Asp
        115                 120                 125

Arg Glu Tyr Asp Phe Arg Asp Leu Thr Trp Cys Ile Asn Pro Pro Glu
    130                 135                 140

Arg Ile Lys Leu Asp Tyr Asp Gln Tyr Cys Ala Asp Val Ala Ala Glu
145                 150                 155                 160

Glu Leu Met Asn Ala Leu Val Asn Ser Thr Leu Leu Glu Thr Arg Ala
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                165                 170                 175

Thr Asn Gln Phe Leu Ala Val Ser Lys Gly Asn Cys Ser Gly Pro Thr
            180                 185                 190

Thr Ile Arg Gly Gln Phe Ser Asn Met Ser Leu Ser Leu Leu Asp Leu
        195                 200                 205

Tyr Leu Ser Arg Gly Tyr Asn Val Ser Ser Ile Val Thr Met Thr Ser
    210                 215                 220

Gln Gly Met Tyr Gly Gly Thr Tyr Leu Val Glu Lys Pro Asn Leu Ser
225                 230                 235                 240

Ser Lys Gly Ser Glu Leu Ser Gln Leu Ser Met His Arg Val Phe Glu
                245                 250                 255

Val Gly Val Ile Arg Asn Pro Gly Leu Gly Ala Pro Val Phe His Met
            260                 265                 270

Thr Asn Tyr Leu Glu Gln Pro Val Ser Asn Asp Phe Ser Asn Cys Met
        275                 280                 285

Val Ala Leu Gly Glu Leu Lys Phe Ala Ala Leu Cys His Arg Glu Asp
    290                 295                 300

Ser Ile Thr Ile Pro Tyr Gln Gly Ser Gly Lys Gly Val Ser Phe Gln
305                 310                 315                 320

Leu Val Lys Leu Gly Val Trp Lys Ser Pro Thr Asp Met Gln Ser Trp
                325                 330                 335

Val Pro Leu Ser Thr Asp Asp Pro Val Ile Asp Arg Leu Tyr Leu Ser
            340                 345                 350

Ser His Arg Gly Val Ile Ala Asp Asn Gln Ala Lys Trp Ala Val Pro
        355                 360                 365

Thr Thr Arg Thr Asp Asp Lys Leu Arg Met Glu Thr Cys Phe Gln Gln
    370                 375                 380

Ala Cys Lys Gly Lys Ile Gln Ala Leu Cys Glu Asn Pro Glu Trp Thr
385                 390                 395                 400

Pro Leu Lys Asp Asn Arg Ile Pro Ser Tyr Gly Val Leu Ser Val Asp
                405                 410                 415

Leu Ser Leu Thr Val Glu Leu Lys Ile Lys Ile Val Ser Gly Phe Gly
            420                 425                 430

Pro Leu Ile Thr His Gly Ser Gly Met Asp Leu Tyr Lys Ser Asn His
        435                 440                 445

Asn Asn Met Tyr Trp Leu Thr Ile Pro Pro Met Lys Asn Leu Ala Leu
    450                 455                 460

Gly Val Ile Asn Thr Leu Glu Trp Ile Pro Arg Phe Lys Val Ser Pro
465                 470                 475                 480

Asn Leu Phe Thr Val Pro Ile Lys Glu Ala Gly Glu Asp Cys His Ala
                485                 490                 495

Pro Thr Tyr Leu Pro Ala Glu Val Asp Gly Asp Val Lys Leu Ser Ser
            500                 505                 510

Asn Leu Val Ile Leu Pro Gly Gln Asp Leu Gln Tyr Val Leu Ala Thr
        515                 520                 525

Tyr Asp Thr Ser Arg Val Glu His Ala Val Val Tyr Tyr Val Tyr Ser
    530                 535                 540

Pro Ser Arg Ser Phe Ser Tyr Phe Tyr Pro Phe Arg Leu Pro Val Arg
545                 550                 555                 560

Gly Val Pro Ile Glu Leu Gln Val Glu Cys Phe Thr Trp Asp Gln Lys
                565                 570                 575

Leu Trp Cys Arg His Phe Cys Val Leu Ala Asp Ser Glu Ser Gly Gly
            580                 585                 590
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His Ile Thr His Ser Gly Met Val Gly Met Gly Val Ser Cys Thr Ala
        595                 600                 605

Thr Arg Glu Asp Gly Thr Ser Arg Arg
    610                 615


<210> SEQ ID NO 51
<211> LENGTH: 1729
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 51

tcaagctttt ggaccctcgt acagaagcta atacgactca ctatagggaa ataagagaga     60

aaagaagagt aagaagaaat ataagagcca ccatggcaca agtcattaat acaaacagcc    120

tgtcgctgtt gacccagaat aacctgaaca aatcccagtc cgcactgggc actgctatcg    180

agcgtttgtc ttccggtctg cgtatcaaca gcgcgaaaga cgatgcggca ggacaggcga    240

ttgctaaccg ttttaccgcg aacatcaaag gtctgactca ggcttcccgt aacgctaacg    300

acggtatctc cattgcgcag accactgaag gcgcgctgaa cgaaatcaac aacaacctgc    360

agcgtgtgcg tgaactggcg gttcagtctg cgaatggtac taactcccag tctgacctcg    420

actccatcca ggctgaaatc acccagcgcc tgaacgaaat cgaccgtgta tccggccaga    480

ctcagttcaa cggcgtgaaa gtcctggcgc aggacaacac cctgaccatc caggttggtg    540

ccaacgacgg tgaaactatc gatattgatt taaaagaaat cagctctaaa acactgggac    600

ttgataagct taatgtccaa gatgcctaca ccccgaaaga aactgctgta accgttgata    660

aaactaccta taaaaatggt acagatccta ttacagccca gagcaatact gatatccaaa    720

ctgcaattgg cggtggtgca acgggggtta ctggggctga tatcaaattt aaagatggtc    780

aatactattt agatgttaaa ggcggtgctt ctgctggtgt ttataaagcc acttatgatg    840

aaactacaaa gaaagttaat attgatacga ctgataaaac tccgttggca actgcggaag    900

ctacagctat tcggggaacg gccactataa cccacaacca aattgctgaa gtaacaaaag    960

agggtgttga tacgaccaca gttgcggctc aacttgctgc agcaggggtt actggcgccg   1020

ataaggacaa tactagcctt gtaaaactat cgtttgagga taaaaacggt aaggttattg   1080

atggtggcta tgcagtgaaa atgggcgacg atttctatgc cgctacatat gatgagaaaa   1140

caggtgcaat tactgctaaa accactactt atacagatgg tactggcgtt gctcaaactg   1200

gagctgtgaa atttggtggc gcaaatggta aatctgaagt tgttactgct accgatggta   1260

agacttactt agcaagcgac cttgacaaac ataacttcag aacaggcggt gagcttaaag   1320

aggttaatac agataagact gaaaacccac tgcagaaaat tgatgctgcc ttggcacagg   1380

ttgatacact tcgttctgac ctgggtgcgg ttcagaaccg tttcaactcc gctatcacca   1440

acctgggcaa taccgtaaat aacctgtctt ctgcccgtag ccgtatcgaa gattccgact   1500

acgcaaccga agtctccaac atgtctcgcg cgcagattct gcagcaggcc ggtacctccg   1560

ttctggcgca ggcgaaccag gttccgcaaa acgtcctctc tttactgcgt tgataatagg   1620

ctggagcctc ggtggccatg cttcttgccc cttgggcctc cccccagccc ctcctcccct   1680

tcctgcaccc gtacccccgt ggtctttgaa taaagtctga gtgggcggc               1729


<210> SEQ ID NO 52
<211> LENGTH: 1518
<212> TYPE: DNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 52

atggcacaag tcattaatac aaacagcctg tcgctgttga cccagaataa cctgaacaaa 60

tcccagtccg cactgggcac tgctatcgag cgtttgtctt ccggtctgcg tatcaacagc 120

gcgaaagacg atgcggcagg acaggcgatt gctaaccgtt ttaccgcgaa catcaaaggt 180

ctgactcagg cttcccgtaa cgctaacgac ggtatctcca ttgcgcagac cactgaaggc 240

gcgctgaacg aaatcaacaa caacctgcag cgtgtgcgtg aactggcggt tcagtctgcg 300

aatggtacta actcccagtc tgacctcgac tccatccagg ctgaaatcac ccagcgcctg 360

aacgaaatcg accgtgtatc cggccagact cagttcaacg gcgtgaaagt cctggcgcag 420

gacaacaccc tgaccatcca ggttggtgcc aacgacggtg aaactatcga tattgattta 480

aaagaaatca gctctaaaac actgggactt gataagctta atgtccaaga tgcctacacc 540

ccgaaagaaa ctgctgtaac cgttgataaa actacctata aaaatggtac agatcctatt 600

acagcccaga gcaatactga tatccaaact gcaattggcg gtggtgcaac gggggttact 660

ggggctgata tcaaatttaa agatggtcaa tactatttag atgttaaagg cggtgcttct 720

gctggtgttt ataaagccac ttatgatgaa actacaaaga aagttaatat tgatacgact 780

gataaaactc cgttggcaac tgcggaagct acagctattc ggggaacggc cactataacc 840

cacaaccaaa ttgctgaagt aacaaaagag ggtgttgata cgaccacagt tgcggctcaa 900

cttgctgcag caggggttac tggcgccgat aaggacaata ctagccttgt aaaactatcg 960

tttgaggata aaaacggtaa ggttattgat ggtggctatg cagtgaaaat gggcgacgat 1020

ttctatgccg ctacatatga tgagaaaaca ggtgcaatta ctgctaaaac cactacttat 1080

acagatggta ctggcgttgc tcaaactgga gctgtgaaat ttggtggcgc aaatggtaaa 1140

tctgaagttg ttactgctac cgatggtaag acttacttag caagcgacct tgacaaacat 1200

aacttcagaa caggcggtga gcttaaagag gttaatacag ataagactga aaacccactg 1260

cagaaaattg atgctgcctt ggcacaggtt gatacacttc gttctgacct gggtgcggtt 1320

cagaaccgtt tcaactccgc tatcaccaac ctgggcaata ccgtaaataa cctgtcttct 1380

gcccgtagcc gtatcgaaga ttccgactac gcaaccgaag tctccaacat gtctcgcgcg 1440

cagattctgc agcaggccgg tacctccgtt ctggcgcagg cgaaccaggt tccgcaaaac 1500

gtcctctctt tactgcgt 1518

<210> SEQ ID NO 53
<211> LENGTH: 1790
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 53

ggggaaauaa gagagaaaag aagaguaaga agaaauauaa gagccaccau ggcacaaguc 60

auuaauacaa acagccuguc gcuguugacc cagaauaacc ugaacaaauc ccaguccgca 120

cugggcacug cuaucgagcg uuugucuucc ggucugcgua ucaacagcgc gaaagacgau 180

gcggcaggac aggcgauugc uaaccguuuu accgcgaaca ucaaaggucu gacucaggcu 240

ucccguaacg cuaacgacgg uaucuccauu gcgcagacca cugaaggcgc gcugaacgaa 300

aucaacaaca accugcagcg ugugcgugaa cuggcgguuc agucugcgaa ugguacuaac 360

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ucccagucug accucgacuc cauccaggcu gaaaucaccc agcgccugaa cgaaaucgac    420

cguguauccg gccagacuca guucaacggc gugaaagucc uggcgcagga caacacccug    480

accauccagg uuggugccaa cgacggugaa acuaucgaua uugauuuaaa agaaaucagc    540

ucuaaaacac ugggacuuga uaagcuuaau guccaagaug ccuacacccc gaaagaaacu    600

gcuguaaccg uugauaaaac uaccuauaaa aaugguacag auccuauuac agcccagagc    660

aauacugaua uccaaacugc aauuggcggu ggugcaacgg ggguuacugg ggcugauauc    720

aaauuuaaag auggucaaua cuauuuagau guuaaaggcg gugcuucugc ugguguuuau    780

aaagccacuu augaugaaac uacaaagaaa guuaauauug auacgacuga uaaaacuccg    840

uuggcaacug cggaagcuac agcuauucgg ggaacggcca cuauaaccca caaccaaauu    900

gcugaaguaa caaaagaggg uguugauacg accacaguug cggcucaacu ugcugcagca    960

gggguuacug gcgccgauaa ggacaauacu agccuuguaa aacuaucguu ugaggauaaa   1020

aacgguaagg uuauugaugg uggcuaugca gugaaaaugg gcgacgauuu cuaugccgcu   1080

acauaugaug agaaaacagg ugcaauuacu gcuaaaacca cuacuuauac agaugguacu   1140

ggcguugcuc aaacuggagc ugugaaauuu gguggcgcaa augguaaauc ugaaguuguu   1200

acugcuaccg augguaagac uuacuuagca agcgaccuug acaaacauaa cuucagaaca   1260

ggcggugagc uuaaagaggu uaauacagau aagacugaaa acccacugca gaaaauugau   1320

gcugccuugg cacagguuga uacacuucgu ucugaccugg gugcgguuca gaaccguuuc   1380

aacuccgcua ucaccaaccu gggcaauacc guaaauaacc ugucuucugc ccguagccgu   1440

aucgaagauu ccgacuacgc aaccgaaguc uccaacaugu cucgcgcgca gauucugcag   1500

caggccggua ccuccguucu ggcgcaggcg aaccagguuc cgcaaaacgu ccucucuuua   1560

cugcguugau aauaggcugg agccucggug gccaugcuuc uugccccuug ggccuccccc   1620

cagccccucc uccccuuccu gcacccguac ccccgugguc uuugaauaaa gucugagugg   1680

gcggcaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa   1740

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaucuag              1790


<210> SEQ ID NO 54
<211> LENGTH: 506
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 54

Met Ala Gln Val Ile Asn Thr Asn Ser Leu Ser Leu Leu Thr Gln Asn
1               5                   10                  15

Asn Leu Asn Lys Ser Gln Ser Ala Leu Gly Thr Ala Ile Glu Arg Leu
            20                  25                  30

Ser Ser Gly Leu Arg Ile Asn Ser Ala Lys Asp Asp Ala Ala Gly Gln
        35                  40                  45

Ala Ile Ala Asn Arg Phe Thr Ala Asn Ile Lys Gly Leu Thr Gln Ala
    50                  55                  60

Ser Arg Asn Ala Asn Asp Gly Ile Ser Ile Ala Gln Thr Thr Glu Gly
65                  70                  75                  80

Ala Leu Asn Glu Ile Asn Asn Asn Leu Gln Arg Val Arg Glu Leu Ala
                85                  90                  95

Val Gln Ser Ala Asn Gly Thr Asn Ser Gln Ser Asp Leu Asp Ser Ile
            100                 105                 110
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Gln Ala Glu Ile Thr Gln Arg Leu Asn Glu Ile Asp Arg Val Ser Gly
        115                 120                 125

Gln Thr Gln Phe Asn Gly Val Lys Val Leu Ala Gln Asp Asn Thr Leu
    130                 135                 140

Thr Ile Gln Val Gly Ala Asn Asp Gly Glu Thr Ile Asp Ile Asp Leu
145                 150                 155                 160

Lys Glu Ile Ser Ser Lys Thr Leu Gly Leu Asp Lys Leu Asn Val Gln
                165                 170                 175

Asp Ala Tyr Thr Pro Lys Glu Thr Ala Val Thr Val Asp Lys Thr Thr
            180                 185                 190

Tyr Lys Asn Gly Thr Asp Pro Ile Thr Ala Gln Ser Asn Thr Asp Ile
        195                 200                 205

Gln Thr Ala Ile Gly Gly Gly Ala Thr Gly Val Thr Gly Ala Asp Ile
    210                 215                 220

Lys Phe Lys Asp Gly Gln Tyr Tyr Leu Asp Val Lys Gly Gly Ala Ser
225                 230                 235                 240

Ala Gly Val Tyr Lys Ala Thr Tyr Asp Glu Thr Thr Lys Lys Val Asn
                245                 250                 255

Ile Asp Thr Thr Asp Lys Thr Pro Leu Ala Thr Ala Glu Ala Thr Ala
            260                 265                 270

Ile Arg Gly Thr Ala Thr Ile Thr His Asn Gln Ile Ala Glu Val Thr
        275                 280                 285

Lys Glu Gly Val Asp Thr Thr Thr Val Ala Ala Gln Leu Ala Ala Ala
    290                 295                 300

Gly Val Thr Gly Ala Asp Lys Asp Asn Thr Ser Leu Val Lys Leu Ser
305                 310                 315                 320

Phe Glu Asp Lys Asn Gly Lys Val Ile Asp Gly Gly Tyr Ala Val Lys
                325                 330                 335

Met Gly Asp Asp Phe Tyr Ala Ala Thr Tyr Asp Glu Lys Thr Gly Ala
            340                 345                 350

Ile Thr Ala Lys Thr Thr Thr Tyr Thr Asp Gly Thr Gly Val Ala Gln
        355                 360                 365

Thr Gly Ala Val Lys Phe Gly Gly Ala Asn Gly Lys Ser Glu Val Val
    370                 375                 380

Thr Ala Thr Asp Gly Lys Thr Tyr Leu Ala Ser Asp Leu Asp Lys His
385                 390                 395                 400

Asn Phe Arg Thr Gly Gly Glu Leu Lys Glu Val Asn Thr Asp Lys Thr
                405                 410                 415

Glu Asn Pro Leu Gln Lys Ile Asp Ala Ala Leu Ala Gln Val Asp Thr
            420                 425                 430

Leu Arg Ser Asp Leu Gly Ala Val Gln Asn Arg Phe Asn Ser Ala Ile
        435                 440                 445

Thr Asn Leu Gly Asn Thr Val Asn Asn Leu Ser Ser Ala Arg Ser Arg
    450                 455                 460

Ile Glu Asp Ser Asp Tyr Ala Thr Glu Val Ser Asn Met Ser Arg Ala
465                 470                 475                 480

Gln Ile Leu Gln Gln Ala Gly Thr Ser Val Leu Ala Gln Ala Asn Gln
                485                 490                 495

Val Pro Gln Asn Val Leu Ser Leu Leu Arg
            500                 505
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<210> SEQ ID NO 55
<211> LENGTH: 698

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 55

Met Ala Gln Val Ile Asn Thr Asn Ser Leu Ser Leu Leu Thr Gln Asn
1 5 10 15

Asn Leu Asn Lys Ser Gln Ser Ala Leu Gly Thr Ala Ile Glu Arg Leu
20 25 30

Ser Ser Gly Leu Arg Ile Asn Ser Ala Lys Asp Asp Ala Ala Gly Gln
35 40 45

Ala Ile Ala Asn Arg Phe Thr Ala Asn Ile Lys Gly Leu Thr Gln Ala
50 55 60

Ser Arg Asn Ala Asn Asp Gly Ile Ser Ile Ala Gln Thr Thr Glu Gly
65 70 75 80

Ala Leu Asn Glu Ile Asn Asn Asn Leu Gln Arg Val Arg Glu Leu Ala
85 90 95

Val Gln Ser Ala Asn Ser Thr Asn Ser Gln Ser Asp Leu Asp Ser Ile
100 105 110

Gln Ala Glu Ile Thr Gln Arg Leu Asn Glu Ile Asp Arg Val Ser Gly
115 120 125

Gln Thr Gln Phe Asn Gly Val Lys Val Leu Ala Gln Asp Asn Thr Leu
130 135 140

Thr Ile Gln Val Gly Ala Asn Asp Gly Glu Thr Ile Asp Ile Asp Leu
145 150 155 160

Lys Gln Ile Asn Ser Gln Thr Leu Gly Leu Asp Thr Leu Asn Val Gln
165 170 175

Gln Lys Tyr Lys Val Ser Asp Thr Ala Ala Thr Val Thr Gly Tyr Ala
180 185 190

Asp Thr Thr Ile Ala Leu Asp Asn Ser Thr Phe Lys Ala Ser Ala Thr
195 200 205

Gly Leu Gly Gly Thr Asp Gln Lys Ile Asp Gly Asp Leu Lys Phe Asp
210 215 220

Asp Thr Thr Gly Lys Tyr Tyr Ala Lys Val Thr Val Thr Gly Gly Thr
225 230 235 240

Gly Lys Asp Gly Tyr Tyr Glu Val Ser Val Asp Lys Thr Asn Gly Glu
245 250 255

Val Thr Leu Ala Gly Gly Ala Thr Ser Pro Leu Thr Gly Gly Leu Pro
260 265 270

Ala Thr Ala Thr Glu Asp Val Lys Asn Val Gln Val Ala Asn Ala Asp
275 280 285

Leu Thr Glu Ala Lys Ala Ala Leu Thr Ala Ala Gly Val Thr Gly Thr
290 295 300

Ala Ser Val Val Lys Met Ser Tyr Thr Asp Asn Asn Gly Lys Thr Ile
305 310 315 320

Asp Gly Gly Leu Ala Val Lys Val Gly Asp Asp Tyr Tyr Ser Ala Thr
325 330 335

Gln Asn Lys Asp Gly Ser Ile Ser Ile Asn Thr Thr Lys Tyr Thr Ala
340 345 350

Asp Asp Gly Thr Ser Lys Thr Ala Leu Asn Lys Leu Gly Gly Ala Asp
355 360 365

Gly Lys Thr Glu Val Val Ser Ile Gly Gly Lys Thr Tyr Ala Ala Ser
370 375 380

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Lys Ala Glu Gly His Asn Phe Lys Ala Gln Pro Asp Leu Ala Glu Ala
385                 390                 395                 400

Ala Ala Thr Thr Thr Glu Asn Pro Leu Gln Lys Ile Asp Ala Ala Leu
                405                 410                 415

Ala Gln Val Asp Thr Leu Arg Ser Asp Leu Gly Ala Val Gln Asn Arg
            420                 425                 430

Phe Asn Ser Ala Ile Thr Asn Leu Gly Asn Thr Val Asn Asn Leu Thr
        435                 440                 445

Ser Ala Arg Ser Arg Ile Glu Asp Ser Asp Tyr Ala Thr Glu Val Ser
    450                 455                 460

Asn Met Ser Arg Ala Gln Ile Leu Gln Gln Ala Gly Thr Ser Val Leu
465                 470                 475                 480

Ala Gln Ala Asn Gln Val Pro Gln Asn Val Leu Ser Leu Leu Arg Gly
                485                 490                 495

Gly Gly Gly Ser Gly Gly Gly Gly Ser Met Met Ala Pro Asp Pro Asn
            500                 505                 510

Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn
        515                 520                 525

Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn
    530                 535                 540

Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn
545                 550                 555                 560

Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn
                565                 570                 575

Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Lys Asn Asn Gln
            580                 585                 590

Gly Asn Gly Gln Gly His Asn Met Pro Asn Asp Pro Asn Arg Asn Val
        595                 600                 605

Asp Glu Asn Ala Asn Ala Asn Asn Ala Val Lys Asn Asn Asn Asn Glu
    610                 615                 620

Glu Pro Ser Asp Lys His Ile Glu Gln Tyr Leu Lys Lys Ile Lys Asn
625                 630                 635                 640

Ser Ile Ser Thr Glu Trp Ser Pro Cys Ser Val Thr Cys Gly Asn Gly
                645                 650                 655

Ile Gln Val Arg Ile Lys Pro Gly Ser Ala Asn Lys Pro Lys Asp Glu
            660                 665                 670

Leu Asp Tyr Glu Asn Asp Ile Glu Lys Lys Ile Cys Lys Met Glu Lys
        675                 680                 685

Cys Ser Ser Val Phe Asn Val Val Asn Ser
    690                 695


<210> SEQ ID NO 56
<211> LENGTH: 692
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 56

Met Met Ala Pro Asp Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala
1               5                   10                  15

Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala
            20                  25                  30

Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala
        35                  40                  45
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Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala
    50                  55                  60

Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala
65                  70                  75                  80

Asn Pro Asn Lys Asn Asn Gln Gly Asn Gly Gln Gly His Asn Met Pro
                85                  90                  95

Asn Asp Pro Asn Arg Asn Val Asp Glu Asn Ala Asn Ala Asn Asn Ala
            100                 105                 110

Val Lys Asn Asn Asn Asn Glu Glu Pro Ser Asp Lys His Ile Glu Gln
        115                 120                 125

Tyr Leu Lys Lys Ile Lys Asn Ser Ile Ser Thr Glu Trp Ser Pro Cys
    130                 135                 140

Ser Val Thr Cys Gly Asn Gly Ile Gln Val Arg Ile Lys Pro Gly Ser
145                 150                 155                 160

Ala Asn Lys Pro Lys Asp Glu Leu Asp Tyr Glu Asn Asp Ile Glu Lys
                165                 170                 175

Lys Ile Cys Lys Met Glu Lys Cys Ser Ser Val Phe Asn Val Val Asn
            180                 185                 190

Ser Arg Pro Val Thr Met Ala Gln Val Ile Asn Thr Asn Ser Leu Ser
        195                 200                 205

Leu Leu Thr Gln Asn Asn Leu Asn Lys Ser Gln Ser Ala Leu Gly Thr
    210                 215                 220

Ala Ile Glu Arg Leu Ser Ser Gly Leu Arg Ile Asn Ser Ala Lys Asp
225                 230                 235                 240

Asp Ala Ala Gly Gln Ala Ile Ala Asn Arg Phe Thr Ala Asn Ile Lys
                245                 250                 255

Gly Leu Thr Gln Ala Ser Arg Asn Ala Asn Asp Gly Ile Ser Ile Ala
            260                 265                 270

Gln Thr Thr Glu Gly Ala Leu Asn Glu Ile Asn Asn Asn Leu Gln Arg
        275                 280                 285

Val Arg Glu Leu Ala Val Gln Ser Ala Asn Ser Thr Asn Ser Gln Ser
    290                 295                 300

Asp Leu Asp Ser Ile Gln Ala Glu Ile Thr Gln Arg Leu Asn Glu Ile
305                 310                 315                 320

Asp Arg Val Ser Gly Gln Thr Gln Phe Asn Gly Val Lys Val Leu Ala
                325                 330                 335

Gln Asp Asn Thr Leu Thr Ile Gln Val Gly Ala Asn Asp Gly Glu Thr
            340                 345                 350

Ile Asp Ile Asp Leu Lys Gln Ile Asn Ser Gln Thr Leu Gly Leu Asp
        355                 360                 365

Thr Leu Asn Val Gln Gln Lys Tyr Lys Val Ser Asp Thr Ala Ala Thr
    370                 375                 380

Val Thr Gly Tyr Ala Asp Thr Thr Ile Ala Leu Asp Asn Ser Thr Phe
385                 390                 395                 400

Lys Ala Ser Ala Thr Gly Leu Gly Gly Thr Asp Gln Lys Ile Asp Gly
                405                 410                 415

Asp Leu Lys Phe Asp Asp Thr Thr Gly Lys Tyr Tyr Ala Lys Val Thr
            420                 425                 430

Val Thr Gly Gly Thr Gly Lys Asp Gly Tyr Tyr Glu Val Ser Val Asp
        435                 440                 445

Lys Thr Asn Gly Glu Val Thr Leu Ala Gly Gly Ala Thr Ser Pro Leu
    450                 455                 460

Thr Gly Gly Leu Pro Ala Thr Ala Thr Glu Asp Val Lys Asn Val Gln
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465                 470                 475                 480

Val Ala Asn Ala Asp Leu Thr Glu Ala Lys Ala Ala Leu Thr Ala Ala
                485                 490                 495

Gly Val Thr Gly Thr Ala Ser Val Val Lys Met Ser Tyr Thr Asp Asn
            500                 505                 510

Asn Gly Lys Thr Ile Asp Gly Gly Leu Ala Val Lys Val Gly Asp Asp
        515                 520                 525

Tyr Tyr Ser Ala Thr Gln Asn Lys Asp Gly Ser Ile Ser Ile Asn Thr
    530                 535                 540

Thr Lys Tyr Thr Ala Asp Asp Gly Thr Ser Lys Thr Ala Leu Asn Lys
545                 550                 555                 560

Leu Gly Gly Ala Asp Gly Lys Thr Glu Val Val Ser Ile Gly Gly Lys
                565                 570                 575

Thr Tyr Ala Ala Ser Lys Ala Glu Gly His Asn Phe Lys Ala Gln Pro
            580                 585                 590

Asp Leu Ala Glu Ala Ala Ala Thr Thr Thr Glu Asn Pro Leu Gln Lys
        595                 600                 605

Ile Asp Ala Ala Leu Ala Gln Val Asp Thr Leu Arg Ser Asp Leu Gly
    610                 615                 620

Ala Val Gln Asn Arg Phe Asn Ser Ala Ile Thr Asn Leu Gly Asn Thr
625                 630                 635                 640

Val Asn Asn Leu Thr Ser Ala Arg Ser Arg Ile Glu Asp Ser Asp Tyr
                645                 650                 655

Ala Thr Glu Val Ser Asn Met Ser Arg Ala Gln Ile Leu Gln Gln Ala
            660                 665                 670

Gly Thr Ser Val Leu Ala Gln Ala Asn Gln Val Pro Gln Asn Val Leu
        675                 680                 685

Ser Leu Leu Arg
    690


<210> SEQ ID NO 57
<211> LENGTH: 1620
<212> TYPE: RNA
<213> ORGANISM: Human metapneumovirus

<400> SEQUENCE: 57

augagcugga agguggugau uaucuucagc cugcugauua caccucaaca cggccugaag     60

gagagcuacc uggaagagag cugcuccacc aucaccgagg gcuaccugag cgugcugcgg    120

accggcuggu acaccaacgu guucacccug gaggugggcg acguggagaa ccugaccugc    180

agcgacggcc cuagccugau caagaccgag cuggaccuga ccaagagcgc ucugagagag    240

cugaagaccg uguccgccga ccagcuggcc agagaggaac agaucgagaa cccucggcag    300

agcagauucg ugcugggcgc caucgcucug ggagucgccg cugccgcugc agugacagcu    360

ggaguggcca uugcuaagac caucagacug gaaagcgagg ugacagccau caacaaugcc    420

cugaagaaga ccaacgaggc cgugagcacc cugggcaaug gagugagagu gcuggccaca    480

gccgugcggg agcugaagga cuucgugagc aagaaccuga ccagagccau caacaagaac    540

aagugcgaca ucgaugaccu gaagauggcc gugagcuucu cccaguucaa cagacgguuc    600

cugaacgugg ugagacaguu cuccgacaac gcuggaauca caccugccau uagccuggac    660

cugaugaccg acgccgagcu ggcuagagcc gugcccaaca ugcccaccag cgcuggccag    720

aucaagcuga ugcuggagaa cagagccaug gugcggagaa agggcuucgg cauccugauu    780

gggguguaug gaagcuccgu gaucuacaug gugcagcugc ccaucuucgg cgugaucgac    840
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acacccugcu ggaucgugaa ggccgcuccu agcugcuccg agaagaaagg aaacuaugcc 900

ugucugcuga gagaggacca gggcugguac ugccagaacg ccggaagcac aguguacuau 960

cccaacgaga aggacugcga gaccagaggc gaccacgugu ucugcgacac cgcugccgga 1020

aucaacgugg ccgagcagag caaggagugc aacaucaaca ucagcacaac caacuacccc 1080

ugcaagguga gcaccggacg gcaccccauc agcauggugg cucugagccc ucugggcgcu 1140

cugguggccu gcuauaaggg cguguccugu agcaucggca gcaaucgggu gggcaucauc 1200

aagcagcuga acaagggaug cuccuacauc accaaccagg acgccgacac cgugaccauc 1260

gacaacaccg uguaccagcu gagcaaggug gagggcgagc agcacgugau caagggcaga 1320

cccgugagcu ccagcuucga ccccaucaag uucccugagg accaguucaa cguggcccug 1380

gaccaggugu uugagaacau cgagaacagc caggcccugg uggaccagag caacagaauc 1440

cuguccagcg cugagaaggg caacaccggc uucaucauug ugaucauucu gaucgccgug 1500

cugggcagcu ccaugauccu ggugagcauc uucaucauua ucaagaagac caagaaaccc 1560

accggagccc cuccugagcu gagcggcgug accaacaaug gcuucauucc ccacaacuga 1620

<210> SEQ ID NO 58
<211> LENGTH: 1620
<212> TYPE: RNA
<213> ORGANISM: Human metapneumovirus

<400> SEQUENCE: 58

augucuugga aagugaugau caucauuucg uuacucauaa caccccagca cgggcuaaag 60

gagaguuauu uggaagaauc auguaguacu auaacugagg gauaccucag uguuuuaaga 120

acaggcuggu acacuaaugu cuucacauua gaaguuggug auguugaaaa ucuuacaugu 180

acugauggac cuagcuuaau caaaacagaa cuugaucuaa caaaaagugc uuuaagggaa 240

cucaaaacag ucucugcuga ucaguuggcg agagaggagc aaauugaaaa ucccagacaa 300

ucaagauuug ucuuaggugc gauagcucuc ggaguugcua cagcagcagc agucacagca 360

ggcauugcaa uagccaaaac cauaaggcuu gagagugagg ugaaugcaau uaaaggugcu 420

cucaaacaaa cuaaugaagc aguauccaca uuagggaaug gugugcgggu ccuagccacu 480

gcagugagag agcuaaaaga auuugugagc aaaaaccuga cuagugcaau caacaggaac 540

aaaugugaca uugcugaucu gaagauggcu gucagcuuca gucaauucaa cagaagauuu 600

cuaaauguug ugcggcaguu uucagacaau gcagggauaa caccagcaau aucauuggac 660

cugaugacug augcugaguu ggccagagcu guaucauaca ugccaacauc ugcagggcag 720

auaaaacuga uguuggagaa ccgcgcaaug guaaggagaa aaggauuugg aauccugaua 780

ggggucuacg gaagcucugu gauuuacaug guucaauugc cgaucuuugg ugucauagau 840

acaccuuguu ggaucaucaa ggcagcuccc ucuugcucag aaaaaaacgg gaauuaugcu 900

ugccuccuaa gagaggauca aggugguau uguaaaaaug caggaucuac uguuuacuac 960

ccaaaugaaa aagacugcga aacaagaggu gaucauguuu uuugugacac agcagcaggg 1020

aucaauguug cugagcaauc aagagaaugc aacaucaaca uaucuacuac caacuaccca 1080

ugcaaaguca gcacaggaag acacccuaua agcaugguug cacuaucacc ucucggugcu 1140

uugguggcuu gcuauaaagg gguaagcugc ucgauuggca gcaauugggu uggaaucauc 1200

aaacaauuac ccaaaggcug cucauacaua accaaccagg augcagacac uguaacaauu 1260

gacaauaccg uguaucaacu aagcaaaguu gaaggugaac agcauguaau aaaagggaga 1320

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ccaguuucaa gcaguuuuga uccaaucaag uuuccugagg aucaguucaa uguugcgcuu 1380

gaucaagucu ucgaaagcau ugagaacagu caggcacuag uggaccaguc aaacaaaauu 1440

cuaaacagug cagaaaaagg aaacacuggu uucauuaucg uaguaauuuu gguugcuguu 1500

cuuggucuaa ccaugauuuc agugagcauc aucaucauaa ucaagaaaac aaggaagccc 1560

acaggagcac cuccagagcu gaaugguguc accaacggcg guuucauacc acauaguuag 1620

<210> SEQ ID NO 59
<211> LENGTH: 1620
<212> TYPE: RNA
<213> ORGANISM: Human metapneumovirus

<400> SEQUENCE: 59

augucuugga aagugaugau uaucauuucg uuacucauaa caccucagca uggacuaaaa 60

gaaaguuauu uagaagaauc auguaguacu auaacugaag gauaucucag uguuuuaaga 120

acagguuggu acaccaaugu cuuuacauua gaaguuggug auguugaaaa ucuuacaugu 180

acugauggac cuagcuuaau caaaacagaa cuugaccuaa ccaaaagugc uuuaagagaa 240

cucaaaacag uuucugcuga ucaguuagcg agagaagaac aaauugaaaa ucccagacaa 300

ucaaggguuug uccuaggugc aauagcucuu ggaguugcca cagcagcagc agucacagca 360

ggcauugcaa uagccaaaac uauaaggcuu gagagugaag ugaaugcaau caaaggugcu 420

cucaaaacaa ccaaugaggc aguaucaaca cuaggaaaug gagugcgggu ccuagccacu 480

gcaguaagag agcugaaaga auuugugagc aaaaaccuga cuagugcgau caacaagaac 540

aagugugaca uugcugauuu gaagauggcu gucagcuuca gucaguucaa cagaagauuc 600

cuaaauguug ugcggcaguu uucagacaau gcagggauaa caccagcaau aucauuggac 660

cugaugaaug augcugagcu ggccagagcu guaucauaca ugccaacauc ugcaggacag 720

auaaaacuaa uguuagagaa ccgugcaaug gugaggagaa aaggauuugg aaucuugaua 780

ggggucuacg gaagcucugu gauuuacaug guccagcugc cgaucuuugg ugucauaaau 840

acaccuuguu ggauaaucaa ggcagcuccc ucuuguucag aaaaagaugg aaauuaugcu 900

ugccuccuaa gagaggauca aggugguguau uguaaaaaug caggauccac uguuuacuac 960

ccaaaugaaa aagacugcga aacaagaggu gaucauguuu uuugugacac agcagcaggg 1020

aucaauguug cugagcaauc aagagaaugc aacaucaaca uaucuaccac caacuaccca 1080

ugcaaaguca gcacaggaag acacccuauc agcaugguug cacuaucacc ucucggugcu 1140

uugguagcuu gcuacaaagg gguuagcugc ucgacuggca guaaucaggu uggaauaauc 1200

aaacaacuac cuaaaggcug cucauacaua acuaaccagg acgcagacac uguaacaauu 1260

gacaacacug uguaucaacu aagcaaaguu gagggugaac agcauguaau aaaagggaga 1320

ccaguuucaa gcaguuuuga uccaaucagg uuuccugagg aucaguucaa uguugcgcuu 1380

gaucaagucu uugaaagcau ugaaaacagu caagcacuag uggaccaguc aaacaaaauu 1440

cugaacagug cagaaaaagg aaacacuggu uucauuauug uaauaauuuu gauugcuguu 1500

cuuggguuaa ccaugauuuc agugagcauc aucaucauaa ucaaaaaaac aaggaagccc 1560

acaggggcac cuccggagcu gaaugguguu accaacggcg guuucauacc gcauaguuag 1620

<210> SEQ ID NO 60
<211> LENGTH: 1725
<212> TYPE: RNA
<213> ORGANISM: Human respiratory syncytial virus

<400> SEQUENCE: 60

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auggaguugc caauccucaa aacaaaugca auuaccacaa uccuugcugc agucacacuc 60

uguuucgcuu ccagucaaaa caucacugaa gaauuuuauc aaucaacaug cagugcaguu 120

agcaaaggcu aucuuagugc ucuaagaacu gguugguaua cuaguguuau aacuauagaa 180

uuaaguaaua ucaaggaaaa uaaguguaau ggaacagaug cuaagguaaa auugauaaaa 240

caagaauuag auaaauauaa aaaugcugua acagaauugc aguugcucau gcaaagcaca 300

ccagcagcca acaaucgagc cagaagagaa cuaccaaggu uuaugaauua uacacucaau 360

aauaccaaaa auaccaaugu aacauuaagc aagaaaagga aaagaagauu ucuuggcuuu 420

uuguuaggug uuggaucugc aaucgccagu ggcauugcug uaucuaaggu ccugcaccua 480

gaaggggaag ugaacaaaau caaaagugcu cuacuaucca caaacaaggc uguagucagc 540

uuaucaaaug gaguuagugu cuuaaccagc aaaguguuag accucaaaaa cuauauagau 600

aaacaguugu uaccuauugu gaacaagcaa agcugcagca uaucaaacau ugaaacugug 660

auagaguucc aacaaaagaa caacagacua cuagagauua ccagggaauu uaguguuaau 720

gcagguguaa cuacaccugu aagcacuuau auguuaacua auagugaauu auuaucauua 780

aucaaugaua ugccuauaac aaaugaucag aaaaaguuaa uguccaacaa uguucaaaua 840

guuagacagc aaaguuacuc uaucaugucc auaauaaagg aggaagucuu agcauaugua 900

guacaauuac cacuauaugg uguaauagau acacccuguu ggaaacugca cacaucccu 960

cuauguacaa ccaacacaaa ggaagggucc aacaucugcu uaacaagaac cgacagagga 1020

ugguauugug acaaugcagg aucaguaucu uucuucccac aagcugaaac auguaaaguu 1080

caaucgaauc ggguauuuug ugacacaaug aacaguuuaa cauuaccaag ugaaguaaau 1140

cucugcaaca uugacauauu caaccccaaa uaugauugca aaauuaugac uucaaaaaca 1200

gauguaagca gcuccguuau cacaucucua ggagccauug ugucaugcua uggcaaaacu 1260

aaauguacag cauccaauaa aaaucguggg aucauaaaga cauuuucuaa cgggugugau 1320

uauguaucaa auaagggggu ggauacugug ucuguaggua auacauuaua uuauguaaau 1380

aagcaagaag gcaaaagucu cuauguaaaa ggugaaccaa uaauaaauuu cuaugaccca 1440

uuaguguucc ccucugauga auuugaugca ucaauaucuc aagucaauga gaagauuaac 1500

cagagccuag cauuuauucg uaaauccgau gaauuauuac auaauguaaa ugcugguaaa 1560

uccaccacaa auaucaugau aacuacuaua auuauaguga uuauaguaau auuguuauca 1620

uuaauugcag uuggacugcu ccuauacugc aaggccagaa gcacaccagu cacacuaagu 1680

aaggaucaac ugagugguau aaauaauauu gcauuuagua acuga 1725

<210> SEQ ID NO 61
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Human parainfluenza virus

<400> SEQUENCE: 61

augccaauuu caauacuguu aauuauuaca accaugauca uggcaucaca cugccaaaua 60

gacaucacaa aacuacagca uguaggugua uuggucaaca gucccaaagg gaugaagaua 120

ucacaaaacu ucgaaacaag auaucuaauc cugagucuca uaccaaaaau agaagauucu 180

aacucuugug gugaccaaca gaucaagcaa uacaagaggu uauuggauag acugaucauu 240

ccuuuauaug auggacuaag auuacagaag gaugugauag ugacuaauca agaauccaau 300

gaaaacacug aucccagaac agaacgauuc uuuggagggg uaauuggaac uauugcucua 360

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ggaguagcaa ccucagcaca aauuacagca gcaguugcuc ugguugaagc caagcaggca 420

agaucagaca uugaaaaacu caaggaagca aucagggaca caaauaaagc agugcaguca 480

guucagagcu cuguaggaaa uuugauagua gcaauuaaau caguccagga uuaugucaac 540

aaagaaaucg ugccaucgau ugcgagacua gguugugaag cagcaggacu ucaguuaggg 600

auugcauuaa cacagcauua cucagaauua acaaauauau uuggugauaa cauaggaucg 660

uuacaagaaa aaggaauaaa auuacaaggu auagcaucau uauaccguac aaauaucaca 720

gaaauauuca caacaucaac aguugacaaa uaugauauuu augaucuauu auuuacagaa 780

ucaauaaagg ugagaguuau agauguugau uugaaugauu acucaauaac ccuccaaguc 840

agacucccuu uauugaccag acugcugaac acucaaaucu acaaaguaga uuccauauca 900

uacaauaucc aaaauagaga augguauauc ccucuuccca gccauaucau gacgaaaggg 960

gcauuucuag guggagcaga ugucaaagaa ugcauagaag cauucagcag uuauauaugc 1020

ccuucugauc caggauuugu acuaaaccau gaaauggaga gcugucuauc aggaaacaua 1080

ucccaauguc caagaaccac agucacauca gacauaguuc cuagguaugc auuugucaau 1140

ggaggagugg uugcgaauug uauaacaacu acauguacau gcaaugguau cgguaauaga 1200

aucaaccaac caccugauca aggagucaaa auuauaacac auaaagaaug uaauacaaua 1260

gguaucaacg gaaugcuauu caacacaaac aaagaaggaa cucuugcauu cuacacacca 1320

gacgacauaa cauuaaacaa uucuguugca cuugauccga uugacauauc aaucgagcuc 1380

aacaaggcca aaucagaucu ugaggaauca aaagaaugga uaagaagguc aaaucaaaag 1440

cuagauucua uuggaaguug gcaucaaucu agcacuacaa ucauaguuau uuugauaaug 1500

augauuauau uguuuauaau uaauauaaca auaauuacaa uugcaauuaa guauuacaga 1560

auucaaaaga gaaaucgagu ggaucaaaau gauaagccgu auguauuaac aaacaag 1617

<210> SEQ ID NO 62
<211> LENGTH: 1716
<212> TYPE: RNA
<213> ORGANISM: Human parainfluenza virus 3

<400> SEQUENCE: 62

auggaauacu ggaagcacac caaccacgga aaggaugcug guaaugagcu ggagacaucc 60

acagccacuc auggcaacaa gcucaccaac aagauaacau auauauugug gacgauaacc 120

cugguguuau uaucaauagu cuucaucaua gugcuaacua auuccaucaa aagugaaaag 180

gcccgcgaau cauugcuaca agacauaaau aaugaguuua uggaaguuac agaaaagauc 240

caaguggcau cggauaauac uaaugaucua auacagucag gagugaauac aaggcuucuu 300

acaauucaga gucaugucca gaauuauaua ccaauaucau ugacacaaca aauaucggau 360

cuuaggaaau ucauuaguga aauuacaauu agaaaugaua aucaagaagu gccaccacaa 420

agaauaacac augauguggg uauaaaaccu uuaaauccag augauuucug gagaugcacg 480

ucuggucuuc caucuuugau gaaaacucca aaaauaagau uaaugccggg accaggauua 540

uuagcuaugc caacgacugu ugauggcugu gucagaaccc cguccuuagu gauaaaugau 600

cugauuuaug cuuacaccuc aaaucuaauu acucgagguu gccaggauau agggaaauca 660

uaucaaguau uacagauagg gauaauaacu guaaacucag acuugguacc ugacuuaaau 720

ccuaggaucu cucauaccuu caacauaaau gacaauagaa agucauguuc ucuagcacuc 780

cuaaauacag auguauauca acuguguuca accccaaaag uugaugaaag aucagauuau 840

gcaucaucag gcauagaaga uauuguacuu gauauuguca auuaugaugg cucaaucucg 900

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acaacaagau uuaagaauaa uaauauaagu uuugaucaac cauaugcggc auuauaccca 960

ucuguuggac cagggauaua cuacaaaggc aaaauaauau uucucgggua uggaggucuu 1020

gaacauccaa uaaaugagaa ugcaaucugc aacacaacug gguguccugg gaaaacacag 1080

agagacugua aucaagcauc ucauagucca ugguuuucag auagaaggau ggucaacucu 1140

auaauuguug uugacaaggg cuugaacuca guuccaaaau ugaagguaug gacgauaucu 1200

augagacaaa auuacugggg gucagaagga agauuacuuc uacuagguaa caagaucuac 1260

auauacacaa gaucuacaag uuggcacagc aaguuacaau uaggaauaau ugacauuacu 1320

gacuacagug auauaaggau aaaauggaca uggcauaaug ugcuaucaag accaggaaac 1380

aaugaauguc caugggaca uucauguccg gauggaugua uaacgggagu auauaccgau 1440

gcauauccac ucaaucccac aggaagcauu guaucaucug ucauauugga cucacaaaaa 1500

ucgagaguca acccagucau aacuuacuca acagcaaccg aaaggguaaa cgagcuggcu 1560

auccgaaaca aaacacucuc agcuggguac acaacaacaa gcugcauuac acacuauaac 1620

aaaggguauu guuuucauau aguagaaaua aaucauaaaa gcuuaaacac auuucaaccc 1680

auguuguuca aaacagagau uccaaaaagc ugcagu 1716

<210> SEQ ID NO 63
<211> LENGTH: 1716
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 63

auggaauacu ggaagcacac caaccacggc aaggacgccg gcaacgagcu ggaaaccagc 60

acagccacac acggcaacaa gcugaccaac aagaucaccu acauccugug gaccaucacc 120

cuggugcugc ugagcaucgu guucaucauc gugcugacca auagcaucaa gagcgagaag 180

gccagagaga gccugcugca ggacaucaac aacgaguuca uggaagugac cgagaagauc 240

cagguggcca gcgacaacac caacgaccug auccagagcg gcgugaacac ccggcugcug 300

accauccaga gccacgugca gaacuacauc cccaucagcc ugacccagca gaucagcgac 360

cugcggaagu ucaucagcga gaucaccauc cggaacgaca accaggaagu gccccccag 420

agaaucaccc acgacguggg caucaagccc cugaaccccg acgauuucug gcgguguaca 480

agcggccugc ccagccugau gaagaccccc aagauccggc ugaugccugg cccuggacug 540

cuggccaugc cuaccacagu ggauggcugu gugcggaccc ccagccucgu gaucaacgau 600

cugaucuacg ccuacaccag caaccugauc acccggggcu gccaggauau cggcaagagc 660

uaccaggugc ugcagaucgg caucaucacc gugaacuccg accuggugcc cgaccugaac 720

ccucggauca gccacaccuu caacaucaac gacaacagaa agagcugcag ccuggcucug 780

cugaacaccg acguguacca gcugugcagc acccccaagg uggacgagag aagcgacuac 840

gccagcagcg gcaucgagga uaucgugcug gacaucguga acuacgacgg cagcaucagc 900

accacccggu ucaagaacaa caacaucagc uucgaccagc ccuacgccgc ccuguacccu 960

ucugugggcc cuggcaucua cuacaagggc aagaucaucu uccugggcua cggcggccug 1020

gaacacccca ucaacgagaa cgccaucugc aacaccaccg gcugcccugg caagacccag 1080

agagacugca aucaggccag ccacagcccc ugguucagcg accgcagaau ggucaacucu 1140

aucaucgugg uggacaaggg ccugaacagc gugcccaagc ugaaagugug gacaaucagc 1200

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augcgccaga acuacugggg cagcgagggc agacuucugc ugcugggaaa caagaucuac 1260

aucuacaccc gguccaccag cuggcacagc aaacugcagc ugggaaucau cgacaucacc 1320

gacuacagcg acauccggau caaguggacc uggcacaacg ugcugagcag acccggcaac 1380

aaugagugcc cuuggggcca cagcugcccc gauggaugua ucaccggcgu guacaccgac 1440

gccuaccccc ugaauccuac cggcuccauc guguccagcg ugauccugga cagccagaaa 1500

agcagaguga accccgugau cacauacagc accgccaccg agagagugaa cgaacuggcc 1560

aucagaaaca agacccugag cgccggcuac accaccacaa gcugcaucac acacuacaac 1620

aagggcuacu gcuuccacau cguggaaauc aaccacaagu cccugaacac cuuccagccc 1680

augcuguuca agaccgagau ccccaagagc ugcucc 1716

<210> SEQ ID NO 64
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 64

augcccauca gcauccugcu gaucaucacc acaaugauca uggccagcca cugccagauc 60

gacaucacca agcugcagca cgugggcgug cucgugaaca gccccaaggg caugaagauc 120

agccagaacu ucgagacacg cuaccugauc cugagccuga uccccaagau cgaggacagc 180

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gagaacaccg acccccggac cgagagauuc uucggcggcg ugaucggcac aaucgcccug 360

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gugcagucca gcgugggcaa ucugaucgug gccaucaagu ccgugcagga cuacgugaac 540

aaagaaaucg ugcccucuau cgcccggcug ggcugugaag cugccggacu gcagcugggc 600

auugcccuga cacagcacua cagcgagcug accaacaucu ucggcgacaa caucggcagc 660

cugcaggaaa agggcauuaa gcugcaggga aucgccagcc uguaccgcac caacaucacc 720

gagaucuuca ccaccagcac cguggauaag uacgacaucu acgaccugcu guucaccgag 780

agcaucaaag ugcgcgugau cgacguggac cugaacgacu acagcaucac ccugcaagug 840

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uacaacaucc agaaccgcga gugguacauc ccucugccca gccacauuau gaccaagggc 960

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cccagcgacc cuggcuucgu gcugaaccac gagauggaaa gcugccugag cggcaacauc 1080

agccagugcc ccagaaccac cgugaccucc gacaucgugc ccagauacgc cuucgugaau 1140

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aacaaggcca agagcgaccu ggaagagucc aaagagugga uccggcggag caaccagaag 1440

cuggacucua ucggcagcug gcaccagagc agcaccacca ucaucgugau ccugauuaug 1500

augauuaucc uguucaucau caacauuacc aucaucacua ucgccauuaa guacuaccgg 1560

auccagaaac ggaaccgggu ggaccagaau gacaagcccu acgugcugac aaacaag 1617

<210> SEQ ID NO 65
<211> LENGTH: 4062
<212> TYPE: RNA
<213> ORGANISM: Middle East respiratory syndrome coronavirus

<400> SEQUENCE: 65

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gauaaaacuu ggccuaggcc aauugauguu ucuaaggcug acgguauuau auacccucaa 180

ggccguacau auucuaacau aacuaucacu uaucaagguc uuuuucccua ucagggagac 240

caugugaua uguauguuua cucugcagga caugcuacag gcacaacucc acaaaaguug 300

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uacacuuaua acauuaccga agaugagauu uuagaguggu uuggcauuac acaaacugcu 780

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uuugccaccu ugccuguuua ugauacuauu aaguauuauu cuaucauucc ucacaguauu 900

cguucuaucc aaagugauag aaaagcuugg gcugccuucu acguauauaa acuucaaccg 960

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aacgguguug gcauuacuca acagguucuu ucagagaacc aaaagcuuau ugccaauaag 3000

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cuugguuuca uugcugggcu uguugccuua gcucuaugcg ucuucuucau acugugcugc 3960

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<210> SEQ ID NO 66
<211> LENGTH: 4062
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 66

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cauggugaua uguauguuua cucugcagga caugcuacag gcacaacucc acaaaaguug 300

uuuguagcua acuauucuca ggacgucaaa caguuugcua auggguuugu cguccguaua 360

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acugguugug gcacaaacug uaugggaaaa cuuaagugua aucguuguug ugauagauac 4020

gaggaauacg accucgagcc gcauaagguu cauguucacu aa 4062

<210> SEQ ID NO 67
<211> LENGTH: 1845
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 67

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uccgugcggu cggugccugg cgaaaugcgg cuggccucca ucgccuucaa ucacccaauc 180

caaguggauc agcugaauag cucguauuuc aagcugucca uccccacgaa cuucucguuc 240

ggggucaccc aggaguacau ccagaccaca auucagaagg ucaccgucga uugcaagcaa 300

uacgugugca acggcuucca gaagugcgag cagcugcuga gagaauacgg gcaguuuugc 360

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gccauugaag aucuucuguu cgacaagguc accaucgccg auccgggcua caugcaggga 600

uacgacgacu guaugcagca gggaccagcc uccgcgaggg accucaucug cgcgcaauac 660

guggccgggu acaaagugcu gccuccucug auggauguga acauggaggc cgcuuauacu 720

ucgucccugc ucggcucuau cgccggcgug ggguggaccg ccggccuguc cuccuucgcc 780

gcuauccccu uugcacaauc cauuuucuac cggcucaacg gcgugggcau uacucaacaa 840

guccugucgg agaaccagaa guugaucgca aacaaguuca aucaggcccu gggggccaug 900

cagacuggau ucacuacgac uaacgaagcg uuccagaagg uccaggacgc ugugaacaac 960

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cuucaacaag uggucaaggc ccugaacgag agcuacaucg accugaagga gcugggcaac 1740

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<210> SEQ ID NO 68
<211> LENGTH: 4071
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 68

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cagaccuuuu ucgacaagac cuggcccaga cccaucgacg uguccaaggc cgacggcauc 180

aucuauccac aaggccggac cuacagcaac aucaccauua ccuaccaggg ccuguuccca 240

uaucaaggcg accacggcga uauguacgug uacucugccg gccacgccac cggcaccaca 300

ccccagaaac uguucguggc caacuacagc caggacguga agcaguucgc caacggcuuc 360

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ccccacagca uccgguccau ccagagcgac agaaaagccu gggccgccuu cuacguguac 960

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uuccagaauu gcacagcagu gggagugcgg cagcagagau ucguguacga ugccuaccag 1920

aaccucgugg gcuacuacag cgacgacggc aauuacuacu gccugcgggc cugugugucc 1980

gugcccgugu ccgugaucua cgacaaagag acaaagaccc acgccacacu guucggcucc 2040

guggccugcg agcacaucag cuccaccaug agccaguacu cccgcuccac ccgguccaug 2100

cugaagcgga gagauagcac cuacggcccc cugcagacac cugugggaug ugugcugggc 2160

cucgugaaca gcucccuguu uguggaagau ugcaagcugc cccugggcca gagccugugu 2220

gcccugccag auaccccuag cacccugacc ccuagaagcg ugcgcucugu gcccggcgaa 2280

augcggcugg ccucuaucgc cuucaaucac cccauccagg uggaccagcu gaacuccagc 2340

uacuucaagc ugagcauccc caccaacuuc agcuucggcg ugacccagga guacauccag 2400

accacaaucc agaaagugac cguggacugc aagcaguacg ugugcaacgg cuuucagaag 2460

ugcgaacagc ugcugcgcga guacggccag uucugcagca agaucaacca ggcccugcac 2520

ggcgccaacc ugagacagga ugacagcgug cggaaccugu ucgccagcgu gaaaagcagc 2580

caguccagcc ccaucauccc uggcuucggc ggcgacuuua accugacccu gcuggaaccu 2640

guguccauca gcaccggcuc cagaagcgcc agauccgcca ucgaggaccu gcuguucgac 2700

aaagugacca uugccgaccc cggcuacaug cagggcuacg acgauugcau gcagcagggc 2760

ccagccagcg ccagggaucu gaucugugcc caguaugugg ccggcuacaa ggugcugccc 2820

ccccugaugg acgugaacau ggaagccgcc uacaccucca gccugcuggg cucuauugcu 2880

ggcgugggau ggacagccgg ccugucuagc uuugccgcca ucccuuucgc ccagagcauc 2940

uucuaccggc ugaacggcgu gggcaucaca caacaggugc ugagcgagaa ccagaagcug 3000

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aucgccaaca aguuuaacca ggcacugggc gccaugcaga ccggcuucac caccaccaac 3060

gaggccuuca gaaaggugca ggacgccgug aacaacaacg cccaggcucu gagcaagcug 3120

gccuccgagc ugagcaauac cuucggcgcc aucagcgccu ccaucggcga caucauccag 3180

cggcuggacg ugcuggaaca ggacgcccag aucgaccggc ugaucaacgg cagacugacc 3240

acccugaacg ccuucguggc acagcagcuc gugcggagcg aaucugccgc ucugucugcu 3300

cagcuggcca aggacaaagu gaacgagugc gugaaggccc aguccaagcg gagcggcuuu 3360

uguggccagg gcacccacau cguguccuuc gucgugaaug cccccaacgg ccuguacuuu 3420

augcacgugg gcuauuaccc cagcaaccac aucgaggugg uguccgccua uggccugugc 3480

gacgccgcca auccuaccaa cuguaucgcc cccgugaacg gcuacuucau caagaccaac 3540

aacacccgga ucguggacga gugguccuac acaggcagca gcuucuacgc ccccgagccc 3600

aucaccuccc ugaacaccaa auacguggcc ccccaaguga cauaccagaa caucuccacc 3660

aaccugcccc cuccacugcu gggaaauucc accggcaucg acuuccagga cgagcuggac 3720

gaguucuuca agaacguguc caccuccauc cccaacuucg gcagccugac ccagaucaac 3780

accacucugc uggaccugac cuacgagaug cugucccugc aacaggucgu gaaagcccug 3840

aacgagagcu acaucgaccu gaaagagcug gggaacuaca ccuacuacaa caaguggccu 3900

ugguacauuu ggcugggcuu uaucgccggc cugguggccc uggcccugug cguguucuuc 3960

auccugugcu gcaccggcug cggcaccaau ugcaugggca agcugaaaug caaccggugc 4020

ugcgacagau acgaggaaua cgaccuggaa ccucacaaag ugcaugugca c 4071

<210> SEQ ID NO 69
<211> LENGTH: 1864
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 69

ucaagcuuuu ggacccucgu acagaagcua auacgacuca cuauagggaa auaagagaga 60

aaagaagagu aagaagaaau auaagagcca ccaugggucu caaggugaac gucucugccg 120

uauucauggc aguacuguua acucuccaaa cacccgccgg ucaaauucau uggggcaauc 180

ucucuaagau agggguagua ggaauaggaa gugcaagcua caaaguuaug acucguucca 240

gccaucaauc auuagucaua aaauuaaugc ccaauauaac ucuccucaau aacugcacga 300

ggguagagau ugcagaauac aggagacuac uaagaacagu uuuggaacca auuagggaug 360

cacuuaaugc aaugacccag aacauaaggc cgguucagag cguagcuuca aguaggagac 420

acaagagauu ugcgggagua guccuggcag gugcggcccu agguguugcc acagcugcuc 480

agauaacagc cggcauugca cuucaccggu ccaugcugaa cucucaggcc aucgacaauc 540

ugagagcgag ccuggaaacu acuaaucagg caauugaggc aaucagacaa gcagggcagg 600

agaugauauu ggcuguucag gguguccaag acuacaucaa uaaugagcug auaccgucua 660

ugaaccagcu aucuugugau cuaaucgguc agaagcucgg gcucaaauug cuuagauacu 720

auacagaaau ccugucauua uuuggcccca gccuacggga ccccauaucu gcggagauau 780

cuauccaggc uuugaguuau gcacuuggag gagauaucaa uaagguguua gaaaagcucg 840

gauacagugg aggcgauuua cuaggcaucu uagagagcag aggaauaaag gcucggauaa 900

cucacgucga cacagagucc uacuucauag uccucaguau agccuauccg acgcuguccg 960

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agauuaaggg ggugauuguc caccggcuag agggggucuc guacaacaua ggcucucaag 1020

agugguauac cacugugccc aaguauguug caacccaagg guaccuuauc ucgaauuuug 1080

augagucauc auguacuuuc augccagagg ggacugugug cagccaaaau gccuuguacc 1140

cgaugagucc ucugcuccaa gaaugccucc ggggguccac caaguccugu gcucguacac 1200

ucguauccgg gucuuuuggg aaccgguuca uuuuaucaca agggaaccua auagccaauu 1260

gugcaucaau ucuuuguaag uguuacacaa cagguacgau uauuaaucaa gacccugaca 1320

agauccuaac auacauugcu gccgaucgcu gcccgguagu cgaggugaac ggcgugacca 1380

uccaagucgg gagcaggagg uauccagacg cuguguacuu gcacagaauu gaccucgguc 1440

cucccauauc auuggagagg uuggacguag ggacaaaucu ggggaaugca auugccaaau 1500

uggaggaugc caaggaauug uuggaaucau cggaccagau auugagaagu augaaagguu 1560

uaucgagcac uagcauaguc uacauccuga uugcagugug ucuuggaggg uugauaggga 1620

uccccacuuu aauauguugc ugcagggggc guuguaacaa aaagggagaa caaguuggua 1680

ugucaagacc aggccuaaag ccugaccuua caggaacauc aaaauccuau guaagaucgc 1740

uuugaugaua auaggcugga gccucggugg ccaagcuucu ugccccuugg gccucccccc 1800

agccccuccu ccccuuccug cacccguacc cccguggucu uugaauaaag ucugaguggg 1860

cggc 1864

<210> SEQ ID NO 70
<211> LENGTH: 1653
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 70

augggucuca aggugaacgu cucugccgua uucauggcag uacuguuaac ucuccaaaca 60

cccgccgguc aaauucauug gggcaaucuc ucuaagauag ggguaguagg aauaggaagu 120

gcaagcuaca aaguuaugac ucguuccagc caucaaucau uagucauaaa auuaaugccc 180

aauauaacuc uccucaauaa cugcacgagg guagagauug cagaauacag gagacuacua 240

agaacaguuu uggaaccaau uagggaugca cuuaaugcaa ugacccagaa cauaaggccg 300

guucagagcg uagcuucaag uaggagacac aagagauuug cgggaguagu ccuggcaggu 360

gcggcccuag guguugccac agcugcucag auaacagccg gcauugcacu ucaccggucc 420

augcugaacu cucaggccau cgacaaucug agagcgagcc uggaaacuac uaaucaggca 480

auugaggcaa ucagacaagc agggcaggag augauauugg cuguucaggg uguccaagac 540

uacaucaaua augagcugau accgucuaug aaccagcuau cuugugaucu aaucggucag 600

aagcucgggc ucaaauugcu uagauacuau acagaaaucc ugucauuauu uggccccagc 660

cuacgggacc ccauaucugc ggagauaucu auccaggcuu ugaguuaugc acuuggagga 720

gauaucaaua agguguuaga aaagcucgga uacaguggag gcgauuuacu aggcaucuua 780

gagagcagag gaauaaaggc ucggauaacu cacgucgaca cagaguccua cuucauaguc 840

cucaguauag ccuauccgac gcuguccgag auuaaggggg ugauugucca ccggcuagag 900

ggggucucgu acaacauagg cucucaagag ugguauacca cugugcccaa guauguugca 960

acccaagggu accuuaucuc gaauuuugau gagucaucau guacuuucau gccagagggg 1020

acugugugca gccaaaaugc cuuguacccg augaguccuc ugcuccaaga augccuccgg 1080

ggguccacca aguccugugc ucguacacuc guauccgggu cuuuugggaa ccgguucauu 1140

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uuaucacaag ggaaccuaau agccaauugu gcaucaauuc uuuguaagug uuacacaaca 1200

gguacgauua uuaaucaaga cccugacaag auccuaacau acauugcugc cgaucgcugc 1260

ccgguagucg aggugaacgg cgugaccauc caagucggga gcaggaggua uccagacgcu 1320

guguacuugc acagaauuga ccucgguccu cccauaucau uggagagguu ggacguaggg 1380

acaaaucugg ggaaugcaau ugccaaauug gaggaugcca aggaauuguu ggaaucaucg 1440

gaccagauau ugagaaguau gaaagguuua ucgagcacua gcauagucua cauccugauu 1500

gcaguguguc uuggaggguu gauagggauc cccacuuuaa uauguugcug caggggggcgu 1560

uguaacaaaa agggagaaca aguugguaug ucaagaccag gccuaaagcc ugaccuuaca 1620

ggaacaucaa aauccuaugu aagaucgcuu uga 1653

<210> SEQ ID NO 71
<211> LENGTH: 1925
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 71

ggggaaauaa gagagaaaag aagaguaaga agaaauauaa gagccaccau gggucucaag 60

gugaacgucu cugccguauu cauggcagua cuguuaacuc uccaaacacc cgccggucaa 120

auucauuggg gcaaucucuc uaagauaggg guaguaggaa uaggaagugc aagcuacaaa 180

guuaugacuc guuccagcca ucaaucauua gucauaaaau uaaugcccaa uauaacucuc 240

cucaauaacu gcacgagggu agagauugca gaauacagga gacuacuaag aacaguuuug 300

gaaccaauua gggaugcacu uaaugcaaug acccagaaca uaaggccggu ucagagcgua 360

gcuucaagua ggagacacaa gagauuugcg ggaguagucc uggcaggugc ggcccuaggu 420

guugccacag cugcucagau aacagccggc auugcacuuc accgguccau gcugaacucu 480

caggccaucg acaaucugag agcgagccug gaaacuacua aucaggcaau ugaggcaauc 540

agacaagcag ggcaggagau gauauuggcu guucagggug uccaagacua caucaauaau 600

gagcugauac cgucuaugaa ccagcuaucu ugugaucuaa ucggucagaa gcucgggcuc 660

aaauugcuua gauacuauac agaaauccug ucauuauuug gccccagccu acgggacccc 720

auaucugcgg agauaucuau ccaggcuuug aguuaugcac uuggaggaga uaucaauaag 780

guguuagaaa agcucggaua caguggaggc gauuuacuag gcaucuuaga gagcagagga 840

auaaaggcuc ggauaacuca cgucgacaca gaguccuacu ucauaguccu caguauagcc 900

uauccgacgc uguccgagau uaaggggugg auuguccacc ggcuagaggg ggucucguac 960

aacauaggcu cucaagagug guauaccacu gugcccaagu auguugcaac ccaaggguac 1020

cuuaucucga auuuugauga gucaucaugu acuuucaugc cagaggggac ugugugcagc 1080

caaaaugccu uguacccgau gaguccucug cuccaagaau gccuccgggg guccaccaag 1140

uccugugcuc guacacucgu auccgggucu uuugggaacc gguucauuuu aucacaaggg 1200

aaccuaauag ccaauugugc aucaauucuu uguaaguguu acacaacagg uacgauuauu 1260

aaucaagacc cugacaagau ccuaacauac auugcugccg aucgcugccc gguagucgag 1320

gugaacggcg ugaccaucca agucgggagc aggagguauc cagacgcugu guacuugcac 1380

agaauugacc ucgguccucc cauaucauug gagagguugg acguagggac aaaucugggg 1440

aaugcaauug ccaaauugga ggaugccaag gaauuguugg aaucaucgga ccagauauug 1500

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agaaguauga aagguuuauc gagcacuagc auagucuaca uccugauugc agugugucuu 1560

ggaggguuga uagggauccc cacuuuaaua uguugcugca gggggcguug uaacaaaaag 1620

ggagaacaag uugguauguc aagaccaggc cuaaagccug accuuacagg aacaucaaaa 1680

uccuauguaa gaucgcuuug augauaauag gcuggagccu cgguggccaa gcuucuugcc 1740

ccuugggccu ccccccagcc ccuccucccc uuccugcacc cguacccccg uggucuuuga 1800

auaaagucug aguggggcggc aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1860

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1920

ucuag 1925

<210> SEQ ID NO 72
<211> LENGTH: 1864
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 72

ucaagcuuuu ggacccucgu acagaagcua auacgacuca cuauagggaa auaagagaga 60

aaagaagagu aagaagaaau auaagagcca ccaugggucu caaggugaac gucucuguca 120

uauucauggc aguacuguua acucuucaaa cacccaccgg ucaaauccau uggggcaauc 180

ucucuaagau agggguggua gggguaggaa gugcaagcua caaaguuaug acucguucca 240

gccaucaauc auuagucaua aaguuaaugc ccaauauaac ucuccucaac aauugcacga 300

ggguagggau ugcagaauac aggagacuac ugagaacagu ucuggaacca auuagagaug 360

cacuuaaugc aaugacccag aauauaagac cgguucagag uguagcuuca aguaggagac 420

acaagagauu ugcgggaguu guccuggcag gugcggcccu aggcguugcc acagcugcuc 480

aaauaacagc cgguauugca cuucaccagu ccaugcugaa cucucaagcc aucgacaauc 540

ugagagcgag ccuagaaacu acuaaucagg caauugaggc aaucagacaa gcagggcagg 600

agaugauauu ggcuguucag gguguccaag acuacaucaa uaaugagcug auaccgucua 660

ugaaucaacu aucuugugau uuaaucggcc agaagcuagg gcucaaauug cucagauacu 720

auacagaaau ccugucauua uuuggcccca gcuuacggga ccccauaucu gcggagauau 780

cuauccaggc uuugagcuau gcgcuuggag gagauaucaa uaagguguug gaaaagcucg 840

gauacagugg aggugaucua cugggcaucu uagagagcag aggaauaaag gcccggauaa 900

cucacgucga cacagagucc uacuucauug uacucaguau agccuauccg acgcuauccg 960

agauuaaggg ggugauuguc caccggcuag agggggucuc guacaacaua ggcucucaag 1020

agugguauac cacugugccc aaguauguug caacccaagg guaccuuauc ucgaauuuug 1080

augagucauc augcacuuuc augccagagg ggacugugug cagccagaau gccuuguacc 1140

cgaugagucc ucugcuccaa gaaugccucc ggggguccac uaaguccugu gcucguacac 1200

ucguauccgg gucuuucggg aaccgguuca uuuuaucaca ggggaaccua auagccaauu 1260

gugcaucaau ccuuugcaag uguuacacaa caggaacaau cauuaaucaa gacccugaca 1320

agauccuaac auacauugcu gccgaucacu gcccgguggu cgaggugaau ggcgugacca 1380

uccaagucgg gagcaggagg uauccggacg cuguguacuu gcacaggauu gaccucgguc 1440

cucccauauc uuuggagagg uuggacguag ggacaaaucu ggggaaugca auugcuaagu 1500

uggaggaugc caaggaauug uuggagucau cggaccagau auugaggagu augaaagguu 1560

uaucgagcac uaguauaguu uacauccuga uugcagugug ucuuggagga uugauaggga 1620

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uccccgcuuu aauauguugc ugcagggggc guuguaacaa gaagggagaa caaguuggua 1680

ugucaagacc aggccuaaag ccugaucuua caggaacauc aaaauccuau guaaggucac 1740

ucugaugaua auaggcugga gccucggugg ccaagcuucu ugccccuugg gccucccccc 1800

agccccuccu ccccuuccug cacccguacc cccguggucu uugaauaaag ucugaguggg 1860

cggc 1864

<210> SEQ ID NO 73
<211> LENGTH: 1653
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 73

augggucuca aggugaacgu cucugucaua uucauggcag uacuguuaac ucuucaaaca 60

cccaccgguc aaauccauug gggcaaucuc ucuaagauag gggugguagg gguaggaagu 120

gcaagcuaca aaguuaugac ucguuccagc caucaaucau uagucauaaa guuaaugccc 180

aauauaacuc uccucaacaa uugcacgagg guagggauug cagaauacag gagacuacug 240

agaacaguuc uggaaccaau uagagaugca cuuaaugcaa ugacccagaa uauaagaccg 300

guucagagug uagcuucaag uaggagacac aagagauuug cgggaguugu ccuggcaggu 360

gcggcccuag gcguugccac agcugcucaa auaacagccg guauugcacu ucaccagucc 420

augcugaacu cucaagccau cgacaaucug agagcgagcc uagaaacuac uaaucaggca 480

auugaggcaa ucagacaagc agggcaggag augauauugg cuguucaggg uguccaagac 540

uacaucaaua augagcugau accgucuaug aaucaacuau cuugugauuu aaucggccag 600

aagcuagggc ucaaauugcu cagauacuau acagaaaucc ugucauuauu uggccccagc 660

uuacgggacc ccauaucugc ggagauaucu auccaggcuu ugagcuaugc gcuuggagga 720

gauaucaaua agguguugga aaagcucgga uacaguggag gugaucuacu gggcaucuua 780

gagagcagag gaauaaaggc ccggauaacu cacgucgaca cagaguccua cuucauugua 840

cucaguauag ccuauccgac gcuauccgag auuaaggggg ugauugucca ccggcuagag 900

ggggucucgu acaacauagg cucucaagag ugguauacca cugugcccaa guauguugca 960

acccaagggu accuuaucuc gaauuuugau gagucaucau gcacuuucau gccagagggg 1020

acugugugca gccagaaugc cuuguacccg augaguccuc ugcuccaaga augccuccgg 1080

ggguccacua aguccugugc ucguacacuc guauccgggu cuuucgggaa ccgguucauu 1140

uuaucacagg ggaaccuaau agccaauugu gcaucaaucc uuugcaagug uuacacaaca 1200

ggaacaauca uuaaucaaga cccugacaag auccuaacau acauugcugc cgaucacugc 1260

ccgguggucg aggugaaugg cgugaccauc caagucggga gcaggaggua uccggacgcu 1320

guguacuugc acaggauuga ccucgguccu cccauaucuu uggagagguu ggacguaggg 1380

acaaaucugg ggaaugcaau ugcuaaguug gaggaugcca aggaauuguu ggagucaucg 1440

gaccagauau ugaggaguau gaaagguuua ucgagcacua guauaguuua cauccugauu 1500

gcaguguguc uuggaggauu gauagggauc cccgcuuuaa uauguugcug caggggggcgu 1560

uguaacaaga agggagaaca aguugguaug ucaagaccag gccuaaagcc ugaucuuaca 1620

ggaacaucaa aauccuaugu aaggucacuc uga 1653

<210> SEQ ID NO 74

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<211> LENGTH: 1925
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 74

ggggaaauaa gagagaaaag aagaguaaga agaaauauaa gagccaccau gggucucaag 60

gugaacgucu cugucauauu cauggcagua cuguuaacuc uucaaacacc caccggucaa 120

auccauuggg gcaaucucuc uaagauaggg gugguagggg uaggaagugc aagcuacaaa 180

guuaugacuc guuccagcca ucaaucauua gucauaaagu uaaugcccaa uauaacucuc 240

cucaacaauu gcacgagggu agggauugca gaauacagga gacuacugag aacaguucug 300

gaaccaauua gagaugcacu uaaugcaaug acccagaaua uaagaccggu ucagagugua 360

gcuucaagua ggagacacaa gagauuugcg ggaguugucc uggcaggugc ggcccuaggc 420

guugccacag cugcucaaau aacagccggu auugcacuuc accaguccau gcugaacucu 480

caagccaucg acaaucugag agcgagccua gaaacuacua aucaggcaau ugaggcaauc 540

agacaagcag ggcaggagau gauauuggcu guucagggug uccaagacua caucaauaau 600

gagcugauac cgucuaugaa ucaacuaucu ugugauuuaa ucggccagaa gcuagggcuc 660

aaauugcuca gauacuauac agaaauccug ucauuauuug gccccagcuu acgggacccc 720

auaucugcgg agauaucuau ccaggcuuug agcuaugcgc uuggaggaga uaucaauaag 780

guguuggaaa agcucggaua caguggaggu gaucuacugg gcaucuuaga gagcagagga 840

auaaaggccc ggauaacuca cgucgacaca gaguccuacu ucauuguacu caguauagcc 900

uauccgacgc uauccgagau uaaggggugg auuguccacc ggcuagaggg ggucucguac 960

aacauaggcu cucaagagug guauaccacu gugcccaagu auguugcaac ccaaggguac 1020

cuuaucucga auuuugauga gucaucaugc acuuucaugc cagaggggac ugugugcagc 1080

cagaaugccu uguacccgau gaguccucug cuccaagaau gccuccgggg guccacuaag 1140

uccugugcuc guacacucgu auccgggucu uucgggaacc gguucauuuu aucacagggg 1200

aaccuaauag ccaauugugc aucaauccuu ugcaaguguu acacaacagg aacaaucauu 1260

aaucaagacc cugacaagau ccuaacauac auugcugccg aucacugccc gguggucgag 1320

gugaauggcg ugaccaucca agucgggagc aggagguauc cggacgcugu guacuugcac 1380

aggauugacc ucgguccucc cauaucuuug gagagguugg acguagggac aaaucugggg 1440

aaugcaauug cuaaguugga ggaugccaag gaauuguugg agucaucgga ccagauauug 1500

aggaguauga aagguuuauc gagcacuagu auaguuuaca uccugauugc aguguucuu 1560

ggaggauuga uagggauccc cgcuuuaaua uguugcugca gggggcguug uaacaagaag 1620

ggagaacaag uugguauguc aagaccaggc cuaaagccug aucuuacagg aacaucaaaa 1680

uccuauguaa ggucacucug augauaauag gcuggagccu cgguggccaa gcuucuugcc 1740

ccuugggccu ccccccagcc ccuccucccc uuccugcacc cguacccccg uggucuuuga 1800

auaaagucug aguggggcggc aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1860

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1920

ucuag 1925

<210> SEQ ID NO 75
<211> LENGTH: 2065
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 75

ucaagcuuuu ggacccucgu acagaagcua auacgacuca cuauagggaa auaagagaga 60

aaagaagagu aagaagaaau auaagagcca ccaugucacc gcaacgagac cggauaaaug 120

ccuucuacaa agauaacccu uaucccaagg gaaguaggau aguuauuaac agagaacauc 180

uuaugauuga cagacccuau guucugcugg cuguucuguu cgucauguuu cugagcuuga 240

ucggauugcu ggcaauugca ggcauuagac uucaucgggc agccaucuac accgcggaga 300

uccauaaaag ccucaguacc aaucuggaug ugacuaacuc caucgagcau caggucaagg 360

acgugcugac accacucuuu aaaaucaucg gggaugaagu gggccugaga acaccucaga 420

gauucacuga ccuagugaaa uucaucucgg acaagauuaa auuccuuaau ccggauaggg 480

aguacgacuu cagagaucuc acuuggugca ucaacccgcc agagaggauc aaacuagauu 540

augaucaaua cugugcagau guggcugcug aagagcucau gaaugcauug gugaacucaa 600

cucuacugga gaccagaaca accacucagu uccuagcugu cucaaaggga aacugcucag 660

ggcccacuac aaucagaggu caauucucaa acaugucgcu guccuuguug gacuuguacu 720

uaggucgagg uuacaaugug ucaucuauag ucacuaugac aucccaggga auguaugggg 780

gaaccuaccu aguugaaaag ccuaaucuga acagcaaagg gucagaguug ucacaacuga 840

gcauguaccg aguguuugaa guagguguga ucagaaaccc gggguuuggg gcuccggugu 900

uccauaugac aaacuauuuu gagcaaccag ucaguaaugg ucucggcaac uguauggugg 960

cuuuggggga gcucaaacuc gcagcccuuu gucacgggga cgauucuauc auaauucccu 1020

aucagggauc agggaaaggu gucagcuucc agcucgucaa gcuggguguc uggaaauccc 1080

caaccgacau gcaauccugg gucccccuau caacggauga uccaguggua gacaggcuuu 1140

accucucauc ucacagaggu gucaucgcug acaaucaagc aaaaugggcu gucccgacaa 1200

cacgaacaga ugacaaguug cgaauggaga caugcuucca gcaggcgugu aaagguaaaa 1260

uccaagcacu cugcgagaau cccgaguggg uaccauugaa ggauaacagg auuccuucau 1320

acgggguccu gucuguugau cugagucuga cgguugagcu uaaaaucaaa auugcuucgg 1380

gauucgggcc auugaucaca cacggcucag ggauggaccu auacaaaucc aacugcaaca 1440

auguguauug gcugacuauu ccgccaauga gaaaucuagc cuuaggcgua aucaacacau 1500

uggaguggau accgagauuc aagguuaguc ccaaccucuu cacuguccca auuaaggaag 1560

caggcgaaga cugccaugcc ccaacauacc uaccugcgga gguggacggu gaugucaaac 1620

ucaguuccaa ccuggugauu cuaccugguc aagaucucca auauguuuug gcaaccuacg 1680

auaccuccag gguugagcau gcugugguuu auuacguuua cagcccaagc cgcucauuuu 1740

cuuacuuuua uccuuuuagg uugccuauaa aggggguccc aaucgaacua caaguggaau 1800

gcuucacaug ggaucaaaaa cucuggugcc gucacuucug ugugcuugcg gacucagaau 1860

ccgguggacu uaucacucac ucugggaugg ugggcauggg agucagcugc acagcuaccc 1920

gggaagaugg aaccaaucgc agauaaugau aauaggcugg agccucggug gccaagcuuc 1980

uugccccuug ggccuccccc cagccccucc uccccuuccu gcacccguac ccccgugguc 2040

uuugaauaaa gucugagugg gcggc 2065

<210> SEQ ID NO 76
<211> LENGTH: 1854
<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 76

augucaccgc aacgagaccg gauaaaugcc uucuacaaag auaacccuua ucccaaggga 60

aguaggauag uuauuaacag agaacaucuu augauugaca gacccuaugu ucugcuggcu 120

guucuguucg ucauguuucu gagcuugauc ggauugcugg caauugcagg cauuagacuu 180

caucgggcag ccaucuacac cgcggagauc cauaaaagcc ucaguaccaa ucuggaugug 240

acuaacucca ucgagcauca ggucaaggac gugcugacac cacucuuuaa aaucaucggg 300

gaugaagugg gccugagaac accucagaga uucacugacc uagugaaauu caucucggac 360

aagauuaaau uccuuaaucc ggauagggag uacgacuuca gagaucucac uuggugcauc 420

aacccgccag agaggaucaa acuagauuau gaucaauacu gugcagaugu ggcugcugaa 480

gagcucauga augcauuggu gaacucaacu cuacuggaga ccagaacaac cacucaguuc 540

cuagcugucu caaagggaaa cugcucaggg cccacuacaa ucagagguca auucucaaac 600

augucgcugu ccuuguugga cuuguacuua ggucgagguu acaauguguc aucuauaguc 660

acuaugacau cccagggaau guaugggggа accuaccuag uugaaaagcc uaaucugaac 720

agcaaagggu cagaguuguc acaacugagc auguaccgag uguuugaagu aggugugauc 780

agaaacccgg guuugggggc uccgguguuc cauaugacaa acuauuuuga gcaaccaguc 840

aguaaugguc ucggcaacug uaugguggcu uuggggгagc ucaaacucgc agcccuuugu 900

cacggggacg auucuaucau aauucccuau cagggaucag ggaaaggugu cagcuuccag 960

cucgucaagc ugggugucug gaaaucccca accgacaugc aauccugggu ccccuuauca 1020

acggaugauc cagugguaga caggcuuuac cucucaucuc acagaggugu caucgcugac 1080

aaucaagcaa aaugggcugu cccgacaaca cgaacagaug acaaguugcg aauggagaca 1140

ugcuuccagc aggcguguaa agguaaaauc caagcacucu gcgagaaucc cgaguggggua 1200

ccauugaagg auaacaggau uccuucauac gggguccugu cuguugaucu gagucugacg 1260

guugagcuua aaaucaaaau ugcuucggga uucgggccau ugaucacaca cggcucaggg 1320

auggaccuau acaaauccaa cugcaacaau guguauuggc ugacuauucc gccaaugaga 1380

aaucuagccu uaggcguaau caacacauug gaguggauac cgagauucaa gguuaguccc 1440

aaccucuuca cugucccaau uaaggaagca ggcgaagacu gccaugcccc aacauaccua 1500

ccugcggagg uggacgguga ugucaaacuc aguuccaacc uggugauucu accuggucaa 1560

gaucuccaau auguuuuggc aaccuacgau accuccaggg uugagcaugc uguggguuau 1620

uacguuuaca gcccaagccg cucauuuucu uacuuuuauc cuuuuagguu gccuauaaag 1680

ggggucccaa ucgaacuaca aguggaaugc uucacauggg aucaaaaacu cuggugccgu 1740

cacuucugug ugcuugcgga cucagaaucc gguggacuua ucacucacuc ugggauggug 1800

ggcaugggag ucagcugcac agcuacccgg gaagauggaa ccaaucgcag auaa 1854

<210> SEQ ID NO 77
<211> LENGTH: 2126
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 77

ggggaaauaa gagagaaaag aagaguaaga agaaauauaa gagccaccau gucaccgcaa 60

cgagaccgga uaaaugccuu cuacaaagau aacccuuauc ccaagggaag uaggauaguu 120

auuaacagag aacaucuuau gauugacaga cccuauguuc ugcuggcugu ucuguucguc 180

auguuucuga gcuugaucgg auugcuggca auugcaggca uuagacuuca ucgggcagcc 240

aucuacaccg cggagaucca uaaaagccuc aguaccaauc uggaugugac uaacuccauc 300

gagcaucagg ucaaggacgu gcugacacca cucuuuaaaa ucaucgggga ugaagugggc 360

cugagaacac cucagagauu cacugaccua gugaaauuca ucucggacaa gauuaaauuc 420

cuuaauccgg auagggagua cgacuucaga gaucucacuu ggugcaucaa cccgccagag 480

aggaucaaac uagauuauga ucaauacugu gcagaugugg cugcugaaga gcucaugaau 540

gcauugguga acucaacucu acuggagacc agaacaacca cucaguuccu agcugucuca 600

aagggaaacu gcucagggcc cacuacaauc agaggucaau ucucaaacau gucgcugucc 660

uuguuggacu uguacuuagg ucgagguuac aaugugucau cuauagucac uaugacaucc 720

cagggaaugu auggggggaac cuaccuaguu gaaaagccua aucugaacag caaaggguca 780

gaguugucac aacugagcau guaccgagug uuugaaguag gugugaucag aaacccgggu 840

uugggggcuc cgguguucca uaugacaaac uauuuugagc aaccagucag uaauggucuc 900

ggcaacugua ugguggcuuu gggggagcuc aaacucgcag cccuuuguca cggggacgau 960

ucuaucauaa uucccuauca gggaucaggg aaagguguca gcuuccagcu cgucaagcug 1020

ggugucugga aaucccccaac cgacaugcaa uccugggucc ccuuaucaac ggaugaucca 1080

gugguagaca ggcuuuaccu cucaucucac agagguguca ucgcugacaa ucaagcaaaa 1140

ugggcugucc cgacaacacg aacagaugac aaguugcgaa uggagacaug cuuccagcag 1200

gcguguaaag guaaaaucca agcacucugc gagaaucccg aguggguacc auugaaggau 1260

aacaggauuc cuucauacgg gguccugucu guugaucuga gucugacggu ugagcuuaaa 1320

aucaaaauug cuucgggauu cgggccauug aucacacacg gcucagggau ggaccuauac 1380

aaauccaacu gcaacaaugu guauuggcug acuauuccgc caaugagaaa ucuagccuua 1440

ggcguaauca acacauugga guggauaccg agauucaagg uuagucccaa ccucuucacu 1500

gucccaauua aggaagcagg cgaagacugc caugccccaa cauaccuacc ugcggaggug 1560

gacggugaug ucaaacucag uuccaaccug gugauucuac cuggucaaga ucuccaauau 1620

guuuuggcaa ccuacgauac cuccaggguu gagcaugcug ugguuuauua cguuuacagc 1680

ccaagccgcu cauuuucuua cuuuuauccu uuuagguugc cuauaaaggg ggucccaauc 1740

gaacuacaag uggaaugcuu cacaugggau caaaaacucu ggugccguca cuucugugug 1800

cuugcggacu cagaauccgg uggacuuauc acucacucug ggaugguggg caugggaguc 1860

agcugcacag cuacccggga agauggaacc aaucgcagau aaugauaaua ggcuggagcc 1920

ucgguggcca agcuucuugc cccuugggcc ucccccagc cccuccuccc cuuccugcac 1980

ccguaccccc guggucuuug aauaaagucu gagugggcgg caaaaaaaaa aaaaaaaaaa 2040

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2100

aaaaaaaaaa aaaaaaaaaa aucuag 2126

<210> SEQ ID NO 78
<211> LENGTH: 2065
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

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<400> SEQUENCE: 78

ucaagcuuuu ggacccucgu acagaagcua auacgacuca cuauagggaa auaagagaga 60

aaagaagagu aagaagaaau auaagagcca ccaugucacc acaacgagac cggauaaaug 120

ccuucuacaa agacaacccc cauccuaagg gaaguaggau aguuauuaac agagaacauc 180

uuaugauuga uagaccuuau guuuugcugg cuguucuauu cgucauguuu cugagcuuga 240

ucggguugcu agccauugca ggcauuagac uucaucgggc agccaucuac accgcagaga 300

uccauaaaag ccucagcacc aaucuggaug uaacuaacuc aaucgagcau cagguuaagg 360

acgugcugac accacucuuc aagaucaucg gugaugaagu gggcuugagg acaccucaga 420

gauucacuga ccuagugaag uucaucucug acaagauuaa auuccuuaau ccggacaggg 480

aauacgacuu cagagaucuc acuuggugua ucaacccgcc agagagaauc aaauuggauu 540

augaucaaua cugugcagau guggcugcug aagaacucau gaaugcauug gugaacucaa 600

cucuacugga gaccagggca accaaucagu uccuagcugu cucaaaggga aacugcucag 660

ggcccacuac aaucagaggc caauucucaa acaugucgcu gucccuguug gacuuguauu 720

uaagucgagg uuacaaugug ucaucuauag ucacuaugac aucccaggga auguacgggg 780

gaacuuaccu aguggaaaag ccuaaucuga gcagcaaagg gucagaguug ucacaacuga 840

gcaugcaccg aguguuugaa guagguguua ucagaaaucc ggguuugggg gcuccgguau 900

uccauaugac aaacuaucuu gagcaaccag ucaguaauga uuucagcaac ugcauggugg 960

cuuuggggga gcucaaguuc gcagcccucu gucacaggga agauucuauc acaauucccu 1020

aucagggauc agggaaaggu gucagcuucc agcuugucaa gcuagguguc uggaaauccc 1080

caaccgacau gcaauccugg gucccccuau caacggauga uccagugaua gacaggcuuu 1140

accucucauc ucacagaggc guuaucgcug acaaucaagc aaaaugggcu gucccgacaa 1200

cacggacaga ugacaaguug cgaauggaga caugcuucca gcaggcgugu aaggguaaaa 1260

uccaagcacu uugcgagaau cccgagugga caccauugaa ggauaacagg auuccuucau 1320

acggggucuu gucuguugau cugagucuga caguugagcu uaaaaucaaa auuguuucag 1380

gauucgggcc auugaucaca cacgguucag ggauggaccu auacaaaucc aaccacaaca 1440

auauguauug gcugacuauc ccgccaauga agaaccuggc cuuaggugua aucaacacau 1500

uggaguggau accgagauuc aagguuaguc ccaaccucuu cacuguucca auuaaggaag 1560

caggcgagga cugccaugcc ccaacauacc uaccugcgga gguggauggu gaugucaaac 1620

ucaguuccaa ucuggugauu cuaccugguc aagaucucca auauguucug gcaaccuacg 1680

auacuuccag aguugaacau gcuguaguuu auuacguuua cagcccaagc cgcucauuuu 1740

cuuacuuuua uccuuuuagg uugccuguaa gggggguccc cauugaauua caaguggaau 1800

gcuucacaug ggaccaaaaa cucuggugcc gucacuucug ugugcuugcg gacucagaau 1860

cugguggaca uaucacucac ucugggaugg ugggcauggg agucagcugc acagccacuc 1920

gggaagaugg aaccagccgc agauagugau aauaggcugg agccucggug gccaagcuuc 1980

uugccccuug ggccucccccc cagccccucc uccccuuccu gcacccguac ccccgugguc 2040

uuugaauaaa gucugagugg gcggc 2065

<210> SEQ ID NO 79
<211> LENGTH: 1854
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

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<400> SEQUENCE: 79

augucaccac aacgagaccg gauaaaugcc uucuacaaag acaaccccca uccuaaggga 60

aguaggauag uuauuaacag agaacaucuu augauugaua gaccuuaugu uuugcuggcu 120

guucuauucg ucauguuucu gagcuugauc ggguugcuag ccauugcagg cauuagacuu 180

caucgggcag ccaucuacac cgcagagauc cauaaaagcc ucagcaccaa ucuggaugua 240

acuaacucaa ucgagcauca gguuaaggac gugcugacac cacucuucaa gaucaucggu 300

gaugaagugg gcuugaggac accucagaga uucacugacc uagugaaguu caucucugac 360

aagauuaaau uccuuaaucc ggacagggaa uacgacuuca gagaucucac uugguguauc 420

aacccgccag agagaaucaa auuggauuau gaucaauacu gugcagaugu ggcugcugaa 480

gaacucauga augcauuggu gaacucaacu cuacuggaga ccagggcaac caaucaguuc 540

cuagcugucu caaagggaaa cugcucaggg cccacuacaa ucagaggcca auucucaaac 600

augucgcugu cccuguugga cuuguauuua agucgagguu acaauguguc aucuauaguc 660

acuaugacau cccagggaau guacggggga acuuaccuag uggaaaagcc uaaucugagc 720

agcaaagggu cagaguuguc acaacugagc augcaccgag uguuugaagu agguguuauc 780

agaaauccgg guuuggggge uccgguauuc cauaugacaa acuaucuuga gcaaccaguc 840

aguaaugauu ucagcaacug caugguggcu uuggggagc ucaaguucgc agcccucugu 900

cacagggaag auucuaucac aauucccuau cagggaucag ggaaaggugu cagcuuccag 960

cuugucaagc uaggugucug gaaaucccca accgacaugc aauccugggu cccccuauca 1020

acggaugauc cagugauaga caggcuuuac cucucaucuc acagaggcgu uaucgcugac 1080

aaucaagcaa aaugggcugu cccgacaaca cggacagaug acaaguugcg aauggagaca 1140

ugcuuccagc aggcguguaa ggguaaaauc caagcacuuu gcgagaaucc cgaguggaca 1200

ccauugaagg auaacaggau uccuucauac ggggucuugu cuguugaucu gagucugaca 1260

guugagcuua aaaucaaaau uguuucagga uucgggccau ugaucacaca cgguucaggg 1320

auggaccuau acaaauccaa ccacaacaau auguauuggc ugacuauccc gccaaugaag 1380

aaccuggccu uagguguaau caacacauug gaguggauac cgagauucaa gguuagucc 1440

aaccucuuca cuguuccaau uaaggaagca ggcgaggacu gccaugcccc aacauaccua 1500

ccugcggagg uggaugguga ugucaaacuc aguuccaauc uggugauucu accuggucaa 1560

gaucuccaau auguucuggc aaccuacgau acuuccagag uugaacaugc uguaguuuau 1620

uacguuuaca gcccaagccg cucauuuucu uacuuuuauc cuuuuagguu gccuguaagg 1680

ggggucccca uugaauuaca aguggaaugc uucacauggg accaaaaacu cuggugccgu 1740

cacuucugug ugcuugcgga cucagaaucu gguggacaua ucacucacuc ugggauggug 1800

ggcaugggag ucagcugcac agccacucgg gaagauggaa ccagccgcag auag 1854

<210> SEQ ID NO 80
<211> LENGTH: 2126
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 80

ggggaaauaa gagagaaaag aagaguaaga agaaauauaa gagccaccau gucaccacaa 60

cgagaccgga uaaaugccuu cuacaaagac aacccccauc cuaagggaag uaggauaguu 120

-continued

auuaacagag aacaucuuau gauugauaga ccuuauguuu ugcuggcugu ucuauucguc 180

auguuucuga gcuugaucgg guugcuagcc auugcaggca uuagacuuca ucgggcagcc 240

aucuacaccg cagagaucca uaaaagccuc agcaccaauc uggauguaac uaacucaauc 300

gagcaucagg uuaaggacgu gcugacacca cucuucaaga ucaucgguga ugaagugggc 360

uugaggacac cucagagauu cacugaccua gugaaguuca ucucugacaa gauuaaauuc 420

cuuaauccgg acagggaaua cgacuucaga gaucucacuu gguguaucaa cccgccagag 480

agaaucaaau uggauuauga ucaauacugu gcagaugugg cugcugaaga acucaugaau 540

gcauugguga acucaacucu acuggagacc agggcaacca aucaguuccu agcugucuca 600

aagggaaacu gcucagggcc cacuacaauc agaggccaau ucucaaacau gucgcugucc 660

cuguuggacu uguauuuaag ucgagguuac aaugugucau cuauagucac uaugacaucc 720

cagggaaugu acgggggaac uuaccuagug gaaaagccua aucugagcag caaaggguca 780

gaguugucac aacugagcau gcaccgagug uuugaaguag guguuaucag aaauccgggu 840

uuggggguc cgguauucca uaugacaaac uaucuugagc aaccagucag uaaugauuuc 900

agcaacugca ugguggcuuu gggggagcuc aaguucgcag cccucuguca cagggaagau 960

ucuaucacaa uucccuauca gggaucaggg aaagguguca gcuuccagcu ugucaagcua 1020

ggugucugga aaucccccaac cgacaugcaa uccugggucc cccuaucaac ggaugaucca 1080

gugauagaca ggcuuuaccu cucaucucac agaggcguua ucgcugacaa ucaagcaaaa 1140

ugggcugucc cgacaacacg gacagaugac aaguugcgaa uggagacaug cuuccagcag 1200

gcguguaagg guaaaaucca agcacuuugc gagaaucccg aguggacacc auugaaggau 1260

aacaggauuc cuucauacgg ggucuugucu guugaucuga gucugacagu ugagcuuaaa 1320

aucaaaauug uuucaggauu cgggccauug aucacacacg guucagggau ggaccuauac 1380

aaauccaacc acaacaauau guauuggcug acuaucccgc caaugaagaa ccuggccuua 1440

gguguaauca acacauugga guggauaccg agauucaagg uuagucccaa ccucuucacu 1500

guuccaauua aggaagcagg cgaggacugc caugccccaa cauaccuacc ugcggaggug 1560

gauggugaug ucaaacucag uuccaaucug gugauucuac cuggucaaga ucuccaauau 1620

guucuggcaa ccuacgauac uuccagaguu gaacaugcug uaguuuauua cguuuacagc 1680

ccaagccgcu cauuuucuua cuuuuauccu uuuagguugc cuguaagggg ggucccccauu 1740

gaauuacaag uggaaugcuu cacaugggac caaaaacucu ggugccguca cuucugugug 1800

cuugcggacu cagaaucugg uggacauauc acucacucug ggaugguggg caugggaguc 1860

agcugcacag ccacucggga agauggaacc agccgcagau agugauaaua ggcuggagcc 1920

ucgguggcca agcuucuugc cccuugggcc ucccccagc cccuccuccc cuuccugcac 1980

ccguaccccc guggucuuug aauaaagucu gaguggggcgg caaaaaaaaa aaaaaaaaaa 2040

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2100

aaaaaaaaaa aaaaaaaaaa aucuag 2126

<210> SEQ ID NO 81
<211> LENGTH: 1729
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 81

ucaagcuuuu ggacccucgu acagaagcua auacgacuca cuauagggaa auaagagaga 60

-continued

aaagaagagu aagaagaaau auaagagcca ccauggcaca agucauuaau acaaacagcc 120

ugucgcuguu gacccagaau aaccugaaca aaucccaguc cgcacugggc acugcuaucg 180

agcguuuguc uuccggucug cguaucaaca gcgcgaaaga cgaugcggca ggacaggcga 240

uugcuaaccg uuuuaccgcg aacaucaaag gucugacuca ggcuucccgu aacgcuaacg 300

acgguaucuc cauugcgcag accacugaag gcgcgcugaa cgaaaucaac aacaaccugc 360

agcgugugcg ugaacuggcg guucagucug cgaaugguac uaacucccag ucugaccucg 420

acuccaucca ggcugaaauc acccagcgcc ugaacgaaau cgaccgugua uccggccaga 480

cucaguucaa cggcgugaaa guccuggcgc aggacaacac ccugaccauc cagguuggug 540

ccaacgacgg ugaaacuauc gauauugauu uaaaagaaau cagcucuaaa acacugggac 600

uugauaagcu uaauguccaa gaugccuaca ccccgaaaga aacugcugua accguugaua 660

aaacuaccua uaaaaauggu acagauccua uuacagccca gagcaauacu gauauccaaa 720

cugcaauugg cgguggugca acggggguua cuggggcuga uaucaaauuu aaagaugguc 780

aauacuauuu agauguuaaa ggcggugcuu cugcuggugu uuauaaagcc acuuaugaug 840

aaacuacaaa gaaaguuaau auugauacga cugauaaaac uccguuggca acugcggaag 900

cuacagcuau ucggggaacg gccacuauaa cccacaacca aauugcugaa guaacaaaag 960

aggguguuga uacgaccaca guugcggcuc aacuugcugc agcagggguu acuggcgccg 1020

auaaggacaa uacuagccuu guaaaacuau cguuugagga uaaaaacggu aagguuauug 1080

augguggcua ugcagugaaa augggcgacg auuucuaugc cgcuacauau gaugagaaaa 1140

caggugcaau uacugcuaaa accacuacuu auacagaugg uacuggcguu gcucaaacug 1200

gagcugugaa auuugguggc gcaaauggua aaucugaagu uguuacugcu accgauggua 1260

agacuuacuu agcaagcgac cuugacaaac auaacuucag aacaggcggu gagcuuaaag 1320

agguuaauac agauaagacu gaaaacccac ugcagaaaau ugaugcugcc uuggcacagg 1380

uugauacacu ucguucugac cugggugcgg uucagaaccg uuucaacucc gcuaucacca 1440

accugggcaa uaccguaaau aaccugucuu cugcccguag ccguaucgaa gauuccgacu 1500

acgcaaccga agucuccaac augucucgcg cgcagauucu gcagcaggcc gguaccuccg 1560

uucuggcgca ggcgaaccag guuccgcaaa acguccucuc uuuacugcgu ugauaauagg 1620

cuggagccuc gguggccaug cuucuugccc cuugggccuc cccccagccc cuccuccccu 1680

uccugcaccc guacccccgu ggucuuugaa uaaagucuga gugggcggc 1729

<210> SEQ ID NO 82
<211> LENGTH: 1518
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 82

auggcacaag ucauuaauac aaacagccug ucgcuguuga cccagaauaa ccugaacaaa 60

ucccaguccg cacugggcac ugcuaucgag cguuugucuu ccggucugcg uaucaacagc 120

gcgaaagacg augcggcagg acaggcgauu gcuaaccguu uuaccgcgaa caucaaaggu 180

cugacucagg cuucccguaa cgcuaacgac gguaucucca uugcgcagac cacugaaggc 240

gcgcugaacg aaaucaacaa caaccugcag cgugugcgug aacuggcggu ucagucugcg 300

aaugguacua acucccaguc ugaccucgac uccauccagg cugaaaucac ccagcgccug 360

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aacgaaaucg accguguauc cggccagacu caguucaacg gcgugaaagu ccuggcgcag 420

gacaacaccc ugaccaucca gguuggugcc aacgacggug aaacuaucga uauugauuua 480

aaagaaauca gcucuaaaac acugggacuu gauaagcuua auguccaaga ugccuacacc 540

ccgaaagaaa cugcuguaac cguugauaaa acuaccuaua aaaaugguac agauccuauu 600

acagcccaga gcaauacuga uauccaaacu gcaauuggcg guggugcaac ggggguuacu 660

ggggcugaua ucaaauuuaa agauggucaa uacuauuuag auguuaaagg cggugcuucu 720

gcugguguuu auaaagccac uuaugaugaa acuacaaaga aaguuaauau ugauacgacu 780

gauaaaacuc cguuggcaac ugcggaagcu acagcuauuc ggggaacggc cacuauaacc 840

cacaaccaaa uugcugaagu aacaaaagag gguguugaua cgaccacagu ugcggcucaa 900

cuugcugcag caggggguuac uggcgccgau aaggacaaua cuagccuugu aaaacuaucg 960

uuugaggaua aaaacgguaa gguuauugau gguggcuaug cagugaaaau gggcgacgau 1020

uucuaugccg cuacauauga ugagaaaaca ggugcaauua cugcuaaaac cacuacuuau 1080

acagauggua cuggcguugc ucaaacugga gcugugaaau uugguggcgc aaaugguaaa 1140

ucugaaguug uuacugcuac cgaugguaag acuuacuuag caagcgaccu ugacaaacau 1200

aacuucagaa caggcgguga gcuuaaagag guuaauacag auaagacuga aaacccacug 1260

cagaaaauug augcugccuu ggcacagguu gauacacuuc guucugaccu gggugcgguu 1320

cagaaccguu ucaacuccgc uaucaccaac cugggcaaua ccguaaauaa ccugucuucu 1380

gcccguagcc guaucgaaga uuccgacuac gcaaccgaag ucuccaacau gucucgcgcg 1440

cagauucugc agcaggccgg uaccuccguu cuggcgcagg cgaaccaggu uccgcaaaac 1500

guccucucuu uacugcgu 1518

<210> SEQ ID NO 83
<211> LENGTH: 1790
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 83

ggggaaauaa gagagaaaag aagaguaaga agaaauauaa gagccaccau ggcacaaguc 60

auuaauacaa acagccuguc gcuguugacc cagaauaacc ugaacaaauc ccaguccgca 120

cugggcacug cuaucgagcg uuugucuucc ggucugcgua ucaacagcgc gaaagacgau 180

gcggcaggac aggcgauugc uaaccguuuu accgcgaaca ucaaaggucu gacucaggcu 240

ucccguaacg cuaacgacgg uaucuccauu gcgcagacca cugaaggcgc gcugaacgaa 300

aucaacaaca accugcagcg ugugcgugaa cuggcgguuc agucugcgaa ugguacuaac 360

ucccagucug accucgacuc cauccaggcu gaaaucaccc agcgccugaa cgaaaucgac 420

cguguauccg gccagacuca guucaacggc gugaaagucc uggcgcagga caacacccug 480

accauccagg uuggugccaa cgacggugaa acuaucgaua uugauuuaaa agaaaucagc 540

ucuaaaacac ugggacuuga uaagcuuaau guccaagaug ccuacacccc gaaagaaacu 600

gcuguaaccg uugauaaaac uaccuauaaa aaugguacag auccuauuac agcccagagc 660

aauacugaua uccaaacugc aauuggcggu ggugcaacgg ggguuacugg ggcugauauc 720

aaauuuaaag auggucaaua cuauuuagau guuaaaggcg gugcuucugc ugguguuuau 780

aaagccacuu augaugaaac uacaaagaaa guuaauauug auacgacuga uaaaacuccg 840

uuggcaacug cggaagcuac agcuauucgg ggaacggcca cuauaaccca caaccaaauu 900

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gcugaaguaa caaaagaggg uguugauacg accacaguug cggcucaacu ugcugcagca 960

gggguuacug gcgccgauaa ggacaauacu agccuuguaa aacuaucguu ugaggauaaa 1020

aacgguaagg uuauugaugg uggcuaugca gugaaaaugg gcgacgauuu cuaugccgcu 1080

acauaugaug agaaaacagg ugcaauuacu gcuaaaacca cuacuuauac agaugguacu 1140

ggcguugcuc aaacuggagc ugugaaauuu gguggcgcaa augguaaauc ugaaguuguu 1200

acugcuaccg augguaagac uuacuuagca agcgaccuug acaaacauaa cuucagaaca 1260

ggcggugagc uuaaagaggu uaauacagau aagacugaaa acccacugca gaaaauugau 1320

gcugccuugg cacagguuga uacacuucgu ucugaccugg gugcgguuca gaaccguuuc 1380

aacuccgcua ucaccaaccu gggcaauacc guaaauaacc ugucuucugc ccguagccgu 1440

aucgaagauu ccgacuacgc aaccgaaguc uccaacaugu cucgcgcgca gauucugcag 1500

caggccggua ccuccguucu ggcgcaggcg aaccagguuc cgcaaaacgu ccucucuuua 1560

cugcguugau aauaggcugg agccucggug gccaugcuuc uugccccuug ggccucccc 1620

cagccccucc uccccuuccu gcacccguac ccccgugguc uuugaauaaa gucugagugg 1680

gcggcaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1740

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaucuag 1790

<210> SEQ ID NO 84
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Salmonella typhimurium

<400> SEQUENCE: 84

Leu Gln Arg Val Arg Glu Leu Ala Val Gln Ser Ala Asn
1 5 10

<210> SEQ ID NO 85
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 85

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1 5 10 15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
20 25 30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
50 55 60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65 70 75 80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
85 90 95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
100 105 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Cys Lys Thr Ile
115 120 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
130 135 140

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Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Phe
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Leu Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Cys Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 86
<211> LENGTH: 539
<212> TYPE: PRT
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 86

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1 5 10 15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
20 25 30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
50 55 60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65 70 75 80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
85 90 95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
100 105 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Cys Lys Thr Ile
115 120 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
130 135 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145 150 155 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
165 170 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
180 185 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
210 215 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225 230 235 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
245 250 255

Gly Ile Leu Cys Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
260 265 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
275 280 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
290 295 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305 310 315 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
325 330 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
340 345 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
355 360 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
370 375 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile

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385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu His Gln Trp His Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 87
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 87

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Leu Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
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    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 88
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 88

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
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        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Leu Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asn Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460
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Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 89
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 89

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Leu Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Leu Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285
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Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 90
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 90

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Leu Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110
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Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Leu Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asn Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525
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Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 91
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 91

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Pro Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Leu Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350
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Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 92
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 92

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Pro Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Leu Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175
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Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asn Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 93
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 93
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Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                  10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Leu Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
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            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 94
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 94

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Leu Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
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                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 95
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 95

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
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65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Leu Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495
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Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 96
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 96

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Trp Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320
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Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 97
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 97

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Leu Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Leu Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140
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Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Leu Lys Asn Leu Trp Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 98
<211> LENGTH: 539
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 98

```
Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                  10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Pro Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380
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Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 99
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 99

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205
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Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 100
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 100

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30
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Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Pro Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
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    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 101
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 101

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Pro Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
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        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 102
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 102

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
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           100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Pro Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525
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Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 103
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 103

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350
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```
Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asn Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 104
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 104

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175
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Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Gln Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 105
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 105
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Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                  10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Trp Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415
```

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
420 425 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
435 440 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
450 455 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465 470 475 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
485 490 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
500 505 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
515 520 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
530 535

<210> SEQ ID NO 106
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 106

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tctgcaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccttt 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccct gaacaagaac 540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgtgt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcaa cgtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 107
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 107

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tctgcaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac 540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgtgt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagc accagtggca tgtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 108
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 108

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctgc tcaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac 540

aagtgcgaca tccctgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 109
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 109

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctgc tcaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

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```
ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc    420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca    480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac    540

aagtgcgaca tccctgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt    600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac    660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag    720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt    780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac    840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc    900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac    960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga   1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc   1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc   1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc   1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc   1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga   1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgaga accagttcca ggtggccctg   1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc   1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg   1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc   1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac      1617
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<210> SEQ ID NO 110
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 110

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atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa     60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga    120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc    180

tctgatggcc ctagcctgat caagaccgag ctggatctgc tcaagagcgc cctgagagaa    240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc    300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca    360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc    420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca    480

gccgtgcgcg agctgaagga cttcgtgctt aagaacctga cacgggccat taacaagaac    540

aagtgcgaca tccctgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt    600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac    660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag    720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt    780
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```
ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac    840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc    900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac    960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga   1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc   1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc   1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc   1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc   1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga   1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg   1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc   1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg   1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc   1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac      1617


<210> SEQ ID NO 111
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 111

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa     60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga    120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc    180

tctgatggcc ctagcctgat caagaccgag ctggatctgc tcaagagcgc cctgagagaa    240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc    300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca    360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc    420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca    480

gccgtgcgcg agctgaagga cttcgtgctt aagaacctga cacgggccat taacaagaac    540

aagtgcgaca tccctgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt    600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac    660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag    720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt    780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac    840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc    900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac    960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga   1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc   1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc   1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc   1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc   1260
```

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgaga accagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 112
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 112

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg cctgtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctgc tcaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac 540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 113

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<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 113

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg cctgtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctgc tcaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac 540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgaga accagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 114
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 114

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctgc tcaagagcgc cctgagagaa 240

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ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc    300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca    360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc    420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca    480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac    540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt    600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac    660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag    720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt    780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac    840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc    900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac    960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga   1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc   1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc   1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc   1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc   1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga   1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg   1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc   1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg   1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc   1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac      1617
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<210> SEQ ID NO 115
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 115

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atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa     60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga    120

accggctggt acaccaacgt gttcacactg gaagtgggcg acctcgagaa tctgacatgc    180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa    240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc    300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca    360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc    420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca    480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac    540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt    600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac    660
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ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 116
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 116

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgctt aagaacctga cacgggccat taacaagaac 540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

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ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 117
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 117

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctgt ggcgggccat taacaagaac 540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

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accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 118
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 118

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acctcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctgc tcaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgctt aagaacctgt ggcgggccat taacaagaac 540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 119
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 119

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg cctgtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac 540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 120
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 120

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac 540

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aagtgcgaca tccctgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 121
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 121

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac 540

aagtgcccta tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

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atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 122
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 122

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg cctagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac 540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

-continued

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 123
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 123

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac 540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttccc acctatcaag ttccctgagg atcagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 124
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 124

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atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac 540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgaga accagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 125
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 125

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

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ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac 540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctcagg atcagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 126
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 126

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac 540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagtggaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

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tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 127
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 127

augagcugga agguggucau caucuucagc cugcugauca caccucagca cggccugaaa 60

gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaaguggggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucuga ccaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucugcaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccuuu 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggcccu gaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugugu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

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ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucaa cguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 128
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 128

augagcugga agguggucau caucuucagc cugcugauca caccucagca cggccugaaa 60

gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaagugggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucuga ccaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucugcaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugugu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagc accaguggca uguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 129
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 129

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gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaagugggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucugc ucaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucccugaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 130
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 130

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gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaagugggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucugc ucaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucccugaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugaga accaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 131
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 131

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gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaagugggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucugc ucaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugcuu aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucccugaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

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ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 132
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 132

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gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaagugggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucugc ucaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugcuu aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucccugaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

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aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugaga accaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 133
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 133

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gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug ccuguggggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucugc ucaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

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<210> SEQ ID NO 134
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 134

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gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug ccugugggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucugc ucaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugaga accaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 135
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 135

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gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaaguggggcg acgucgagaa ucugacaugc 180

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ucugauggcc cuagccugau caagaccgag cuggaucugc ucaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 136
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 136

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gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaagugggcg accucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucuga ccaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

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cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 137
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 137

augagcugga agguggucau caucuucagc cugcugauca caccucagca cggccugaaa 60

gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaagugggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucuga ccaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugcuu aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

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ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 138
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 138

augagcugga agguggucau caucuucagc cugcugauca caccucagca cggccugaaa 60

gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaaguggggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucuga ccaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucguguc aagaaccugu ggcgggccau uaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

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accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 139
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 139

augagcugga agguggucau caucuucagc cugcugauca caccucagca cggccugaaa 60

gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaagugggcg accucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucugc ucaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugcuu aagaaccugu ggcgggccau uaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 140
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 140

augagcugga agguggucau caucuucagc cugcugauca caccucagca cggccugaaa 60

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gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug ccugugggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucuga ccaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 141
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 141

augagcugga agguggucau caucuucagc cugcugauca caccucagca cggccugaaa 60

gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaaguggggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucuga ccaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac 540

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aagugcgaca ucccugaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu    600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac    660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag    720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu    780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac    840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc    900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac    960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga   1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc   1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc   1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc   1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc   1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga   1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug   1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc   1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug   1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc   1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac      1617
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<210> SEQ ID NO 142
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 142

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gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga    120

accggcuggu acaccaacgu guucacacug gaagugggcg acgucgagaa ucugacaugc    180

ucugauggcc cuagccugau caagaccgag cuggaucuga ccaagagcgc ccugagagaa    240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc    300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca    360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc    420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca    480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac    540

aagugcccua ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu    600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac    660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag    720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu    780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac    840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc    900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac    960
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ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 143
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 143

augagcugga agguggucau caucuucagc cugcugauca caccucagca cggccugaaa 60

gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaagugggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucuga ccaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug ccuagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

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cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 144
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 144

augagcugga agguggucau caucuucagc cugcugauca caccucagca cggccugaaa 60

gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaagugggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucuga ccaagagcgc ccugagagaa 240

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ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

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What is claimed is:

1. A composition, comprising: a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit formulated in a lipid nanoparticle.

2. The composition of claim **1**, wherein the open reading frame encodes a BetaCoV S protein.

3. The composition of claim **1**, wherein the open reading frame encodes an S protein subunit selected from an S1 subunit and an S2 subunit.

4. The composition of claim **1**, wherein the mRNA further comprising a 5' untranslated region (UTR) and a 3' UTR.

5. The composition of claim **4**, wherein the mRNA further comprises a poly(A) tail.

6. The composition of claim **4**, wherein the mRNA further comprises a 5' cap analog.

7. The composition of claim **6**, wherein the 5' cap analog is 7mG(5')ppp(5')NlmpNp.

8. The composition of claim **1**, wherein the mRNA comprises a chemical modification.

9. The composition of claim **8**, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.

10. The composition of claim **8**, wherein at least 80% of the uracil in the open reading frame has a chemical modification.

11. The composition of claim **1**, wherein the lipid nanoparticle comprises an ionizable cationic lipid, a neutral lipid, a sterol, and a PEG-modified lipid.

12. The composition of claim **11**, wherein the lipid nanoparticle comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.

13. The composition of claim **12**, wherein the lipid nanoparticle comprises 50% ionizable cationic lipid, 10% neutral lipid, 38.5% sterol, and 1.5% PEG-modified lipid.

14. The composition of claim **11**, wherein the ionizable cationic lipid is Compound 25.

15. The composition of claim **11**, wherein the neutral lipid is 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), the sterol is cholesterol, and the PEG-modified lipid is 1,2-dimyristoyl-racalycero-3-methoxypolyethylene glycol-2000 (PEG-DMG) or PEG-cDMA.

16. A composition, comprising: a messenger ribonucleic acid (mRNA) comprising a 5' untranslated region (UTR), an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit, a 3' UTR, and a poly(A) tail, formulated in a lipid nanoparticle that comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.

17. The composition of claim **16**, wherein the open reading frame encodes a BetaCoV S protein.

18. The composition of claim **16**, wherein the open reading frame encodes an S protein subunit selected from an S1 subunit and an S2 subunit.

19. The composition of claim **16**, wherein the mRNA further comprises 5' cap analog 7mG(5')ppp(5')NlmpNp.

20. The composition of claim **16**, wherein at least 80% of the uracil in the open reading frame has a chemical modification.

21. The composition of claim **20**, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.

22. The composition of claim **16**, wherein the ionizable cationic lipid is Compound 25.

23. The composition of claim **16**, wherein the neutral lipid is DSPC, the sterol is cholesterol, and the PEG-modified lipid is PEG-DMG.

24. A composition, comprising: a messenger ribonucleic acid (mRNA) comprising a 5' cap analog, a 5' untranslated region (UTR), an open reading frame encoding a betacoronavirus (BetaCoV) S protein, a 3' UTR, and a poly(A) tail, formulated in a lipid nanoparticle that comprises 20-60% ionizable cationic lipid, 5-25% DSPC, 25-55% cholesterol, and 0.5-15% PEG-DMG, wherein the ionizable cationic lipid has the structure of Compound 25, and wherein at least 80% of the uracil in the open reading frame has a 1-methylpseudouridine modification.

25. The composition of claim **24**, wherein the 5' cap analog is 7mG(5')ppp(5')NlmpNp.

26. A lipid nanoparticle, comprising: a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit; wherein the lipid nanoparticle comprises

20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.

* * * * *

EXHIBIT 3

US010933127B2

(12) **United States Patent**
Ciaramella et al.

(10) **Patent No.: US 10,933,127 B2**
(45) **Date of Patent: Mar. 2, 2021**

(54) **BETACORONAVIRUS MRNA VACCINE**

(71) Applicant: **ModernaTX, Inc.**, Cambridge, MA (US)

(72) Inventors: **Giuseppe Ciaramella**, Sudbury, MA (US); **Sunny Himansu**, Winchester, MA (US)

(73) Assignee: **ModernaTX, Inc.**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **16/880,829**

(22) Filed: **May 21, 2020**

(65) **Prior Publication Data**

US 2020/0282046 A1 Sep. 10, 2020

Related U.S. Application Data

(60) Division of application No. 16/805,587, filed on Feb. 28, 2020, now Pat. No. 10,702,600, which is a continuation of application No. 16/368,270, filed on Mar. 28, 2019, now Pat. No. 10,702,599, which is a continuation of application No. 16/040,981, filed on Jul. 20, 2018, now Pat. No. 10,272,150, which is a continuation of application No. 15/674,599, filed on Aug. 11, 2017, now Pat. No. 10,064,934, which is a continuation of application No. PCT/US2016/058327, filed on Oct. 21, 2016.

(60) Provisional application No. 62/247,394, filed on Oct. 28, 2015, provisional application No. 62/247,362, filed on Oct. 28, 2015, provisional application No. 62/247,297, filed on Oct. 28, 2015, provisional application No. 62/247,483, filed on Oct. 28, 2015, provisional application No. 62/244,802, filed on Oct. 22, 2015, provisional application No. 62/245,031, filed on Oct. 22, 2015, provisional application No. 62/244,946, filed on Oct. 22, 2015, provisional application No. 62/244,813, filed on Oct. 22, 2015, provisional application No. 62/244,837, filed on Oct. 22, 2015.

(51) **Int. Cl.**

A61K 39/215	(2006.01)
A61K 39/12	(2006.01)
A61P 11/00	(2006.01)
A61K 39/155	(2006.01)
C07K 16/10	(2006.01)
A61K 39/00	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 39/155*** (2013.01); ***A61K 39/12*** (2013.01); ***A61K 39/215*** (2013.01); ***A61P 11/00*** (2018.01); ***C07K 16/10*** (2013.01); ***C07K 16/1027*** (2013.01); *A61K 2039/53* (2013.01); *A61K 2039/55511* (2013.01); *A61K 2039/55555* (2013.01); *A61K 2039/6018* (2013.01); *A61K 2039/70* (2013.01); *C07K 2317/76* (2013.01); *C12N 2760/18034* (2013.01); *C12N 2760/18334* (2013.01); *C12N 2760/18434* (2013.01); *C12N 2760/18534* (2013.01); *C12N 2760/18634* (2013.01); *C12N 2770/20034* (2013.01); *Y02A 50/30* (2018.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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Primary Examiner — Nicole Kinsey White

(74) *Attorney, Agent, or Firm* — Wolf, Greenfield & Sacks, P.C.

(57) **ABSTRACT**

The disclosure relates to respiratory virus ribonucleic acid (RNA) vaccines and combination vaccines, as well as methods of using the vaccines and compositions comprising the vaccines.

21 Claims, 24 Drawing Sheets

Specification includes a Sequence Listing.

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U.S. Appl. No. 16/623,069, filed Dec. 16, 2019, Hoge et al.
U.S. Appl. No. 16/639,403, filed Feb. 14, 2020, Hoge et al.
U.S. Appl. No. 16/848,318, filed Apr. 14, 2020, Ciaramella et al.
U.S. Appl. No. 16/965,589, filed Jul. 28, 2020, Ciaramella et al.
U.S. Appl. No. 16/608,451, filed Oct. 25, 2019, Ciaramella et al.
U.S. Appl. No. 16/788,182, filed Feb. 11, 2020, Panther et al.
U.S. Appl. No. 16/794,318, filed Feb. 19, 2020, Mauger et al.
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Fig. 1

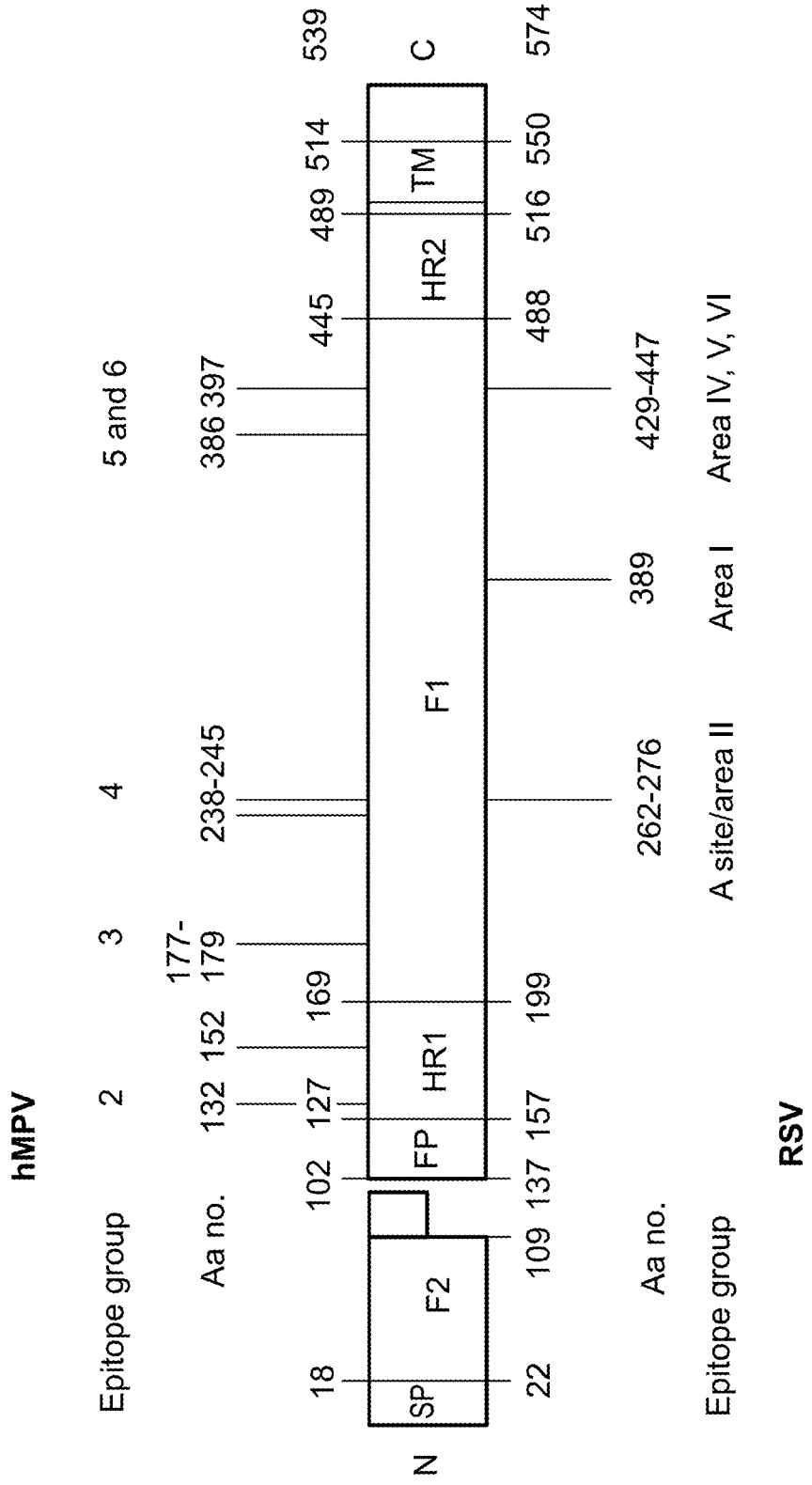

hMPV
Epitope group
2
5 and 6
3
4
Aa no.
132
386 397
177-179
238-245
127
152
169
102
445
514
539
489
516
550
574
488
199
157
137
109
18
22
SP
F2
FP
HR1
F1
HR2
TM
C
N
429-447
389
262-276
Aa no.
Epitope group
Area IV, V, VI
Area I
A site/area II
RSV

Fig. 2A

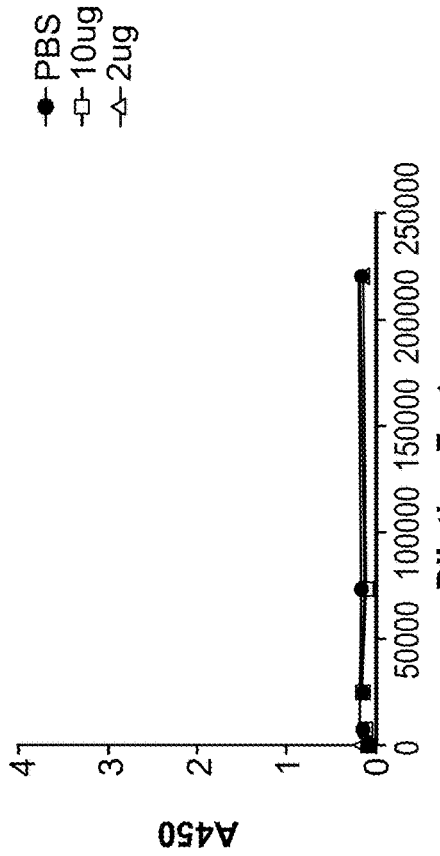


Fig. 2B

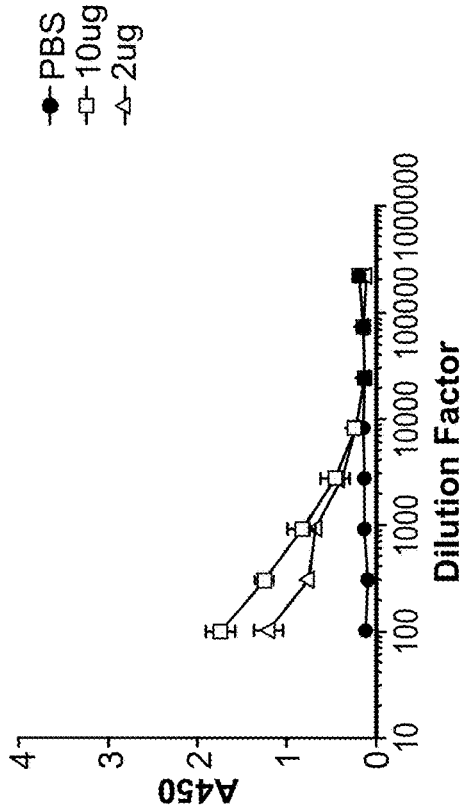


Fig. 2C

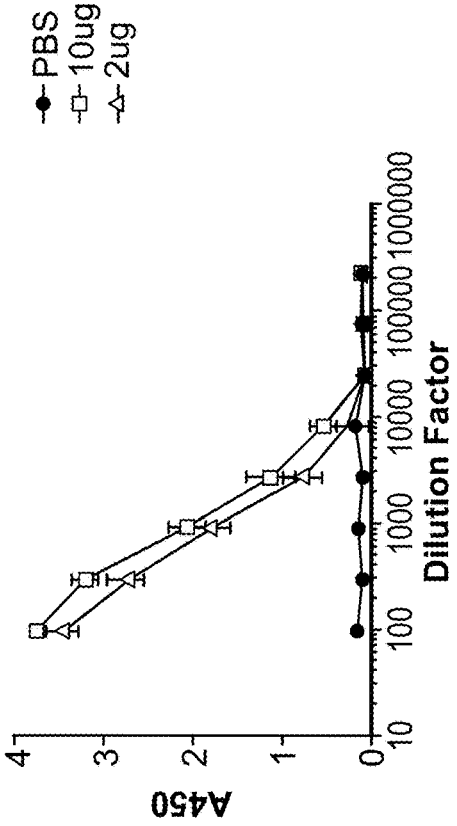


Fig. 3A

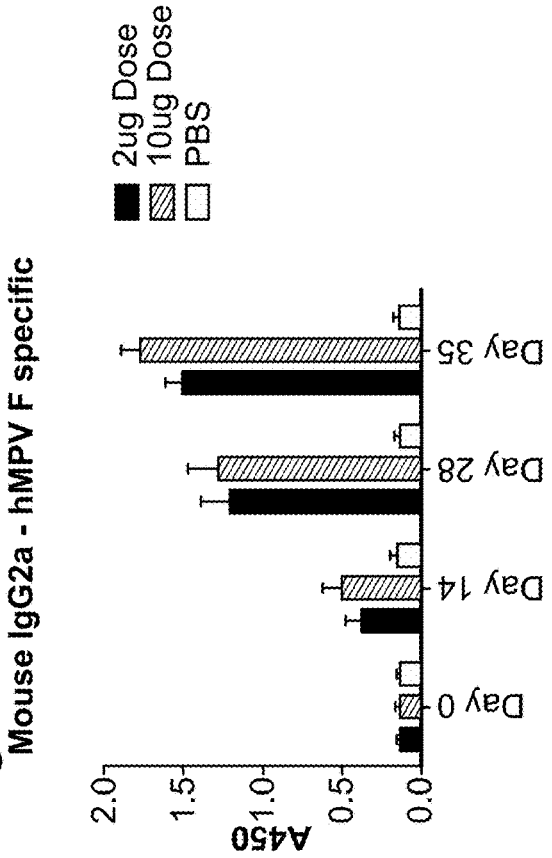


Fig. 3B

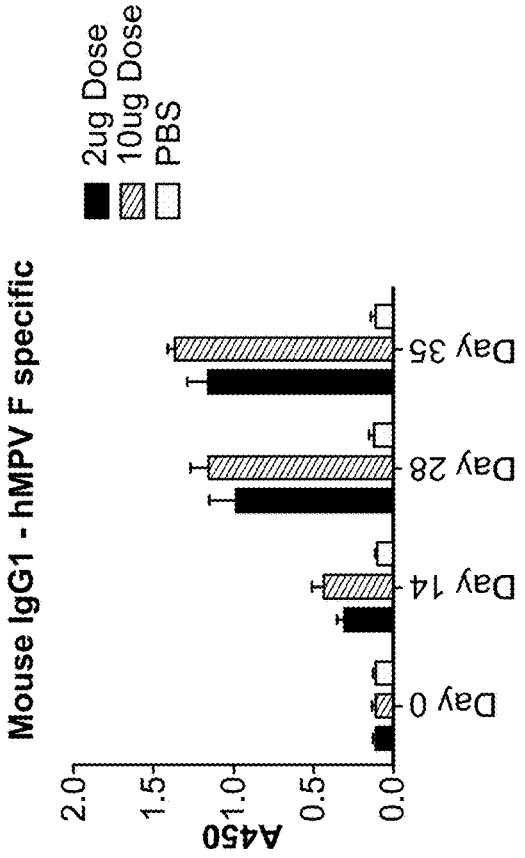


Fig. 3C

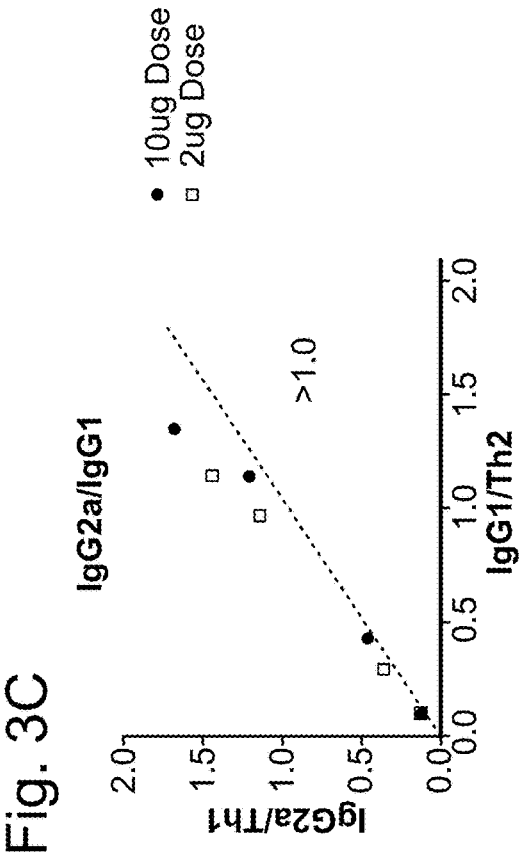
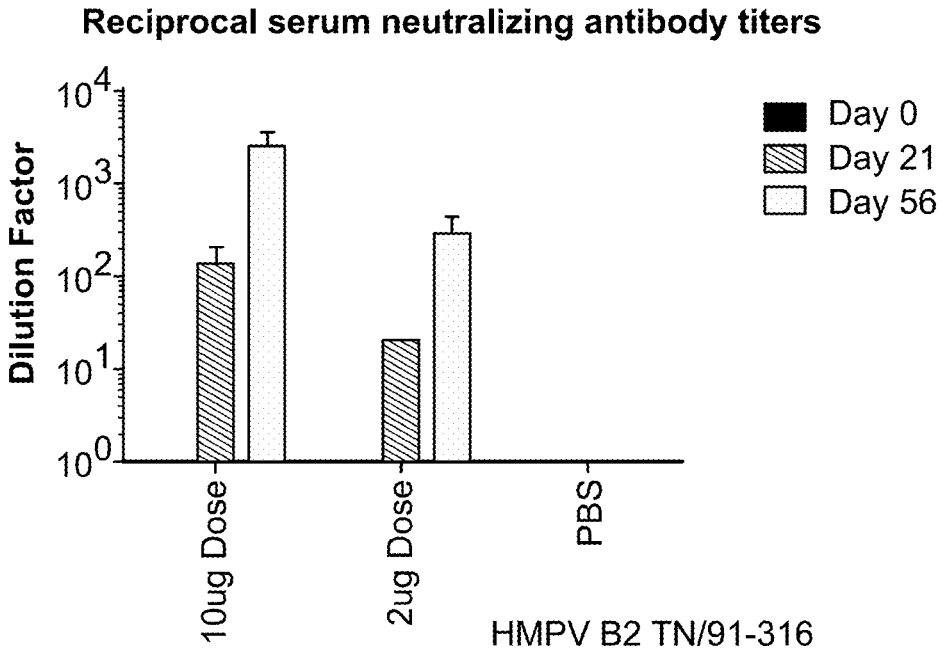


Fig. 4


Reciprocal serum neutralizing antibody titers
Dilution Factor
10^4
10^3
10^2
10^1
10^0
Day 0
Day 21
Day 56
10ug Dose
2ug Dose
PBS
HMPV B2 TN/91-316

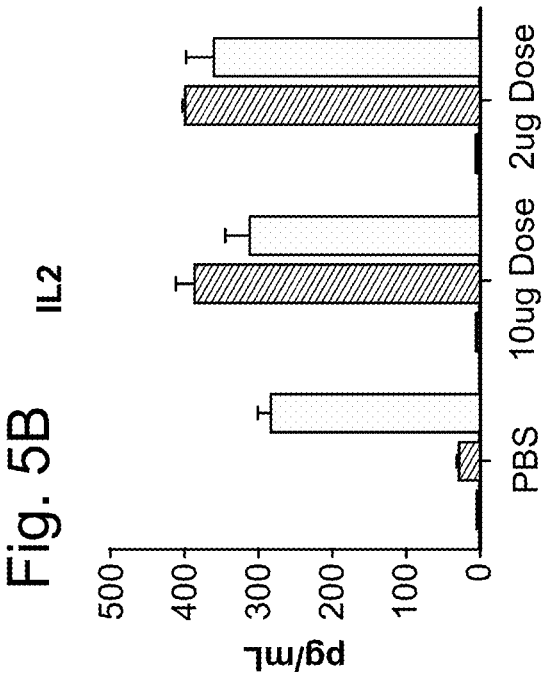
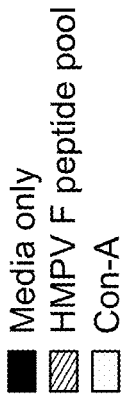


Fig. 5B
IL2
pg/mL
0
100
200
300
400
500
PBS
10ug Dose
2ug Dose


Media only
HMPV F peptide pool
Con-A

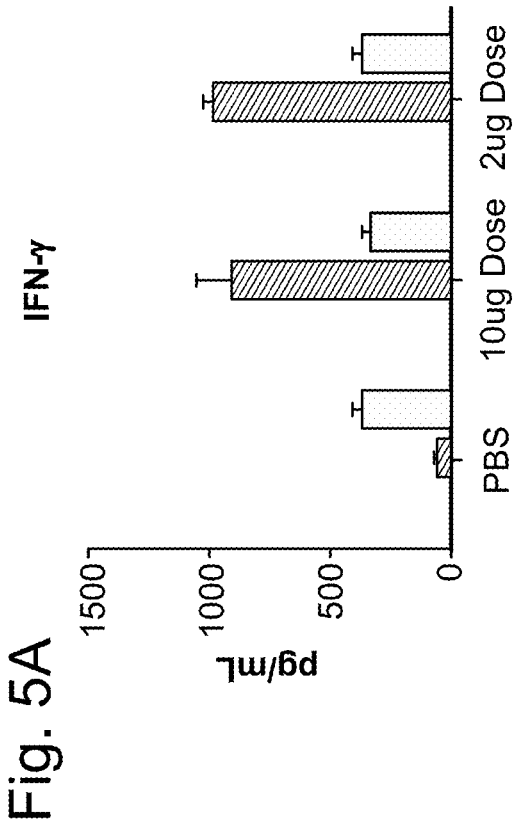


Fig. 5A
IFN-γ
pg/mL
0
500
1000
1500
PBS
10ug Dose
2ug Dose

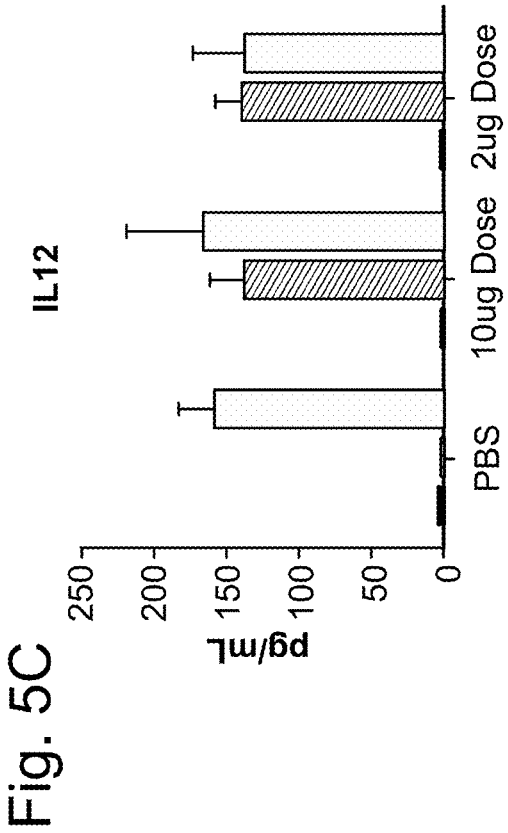
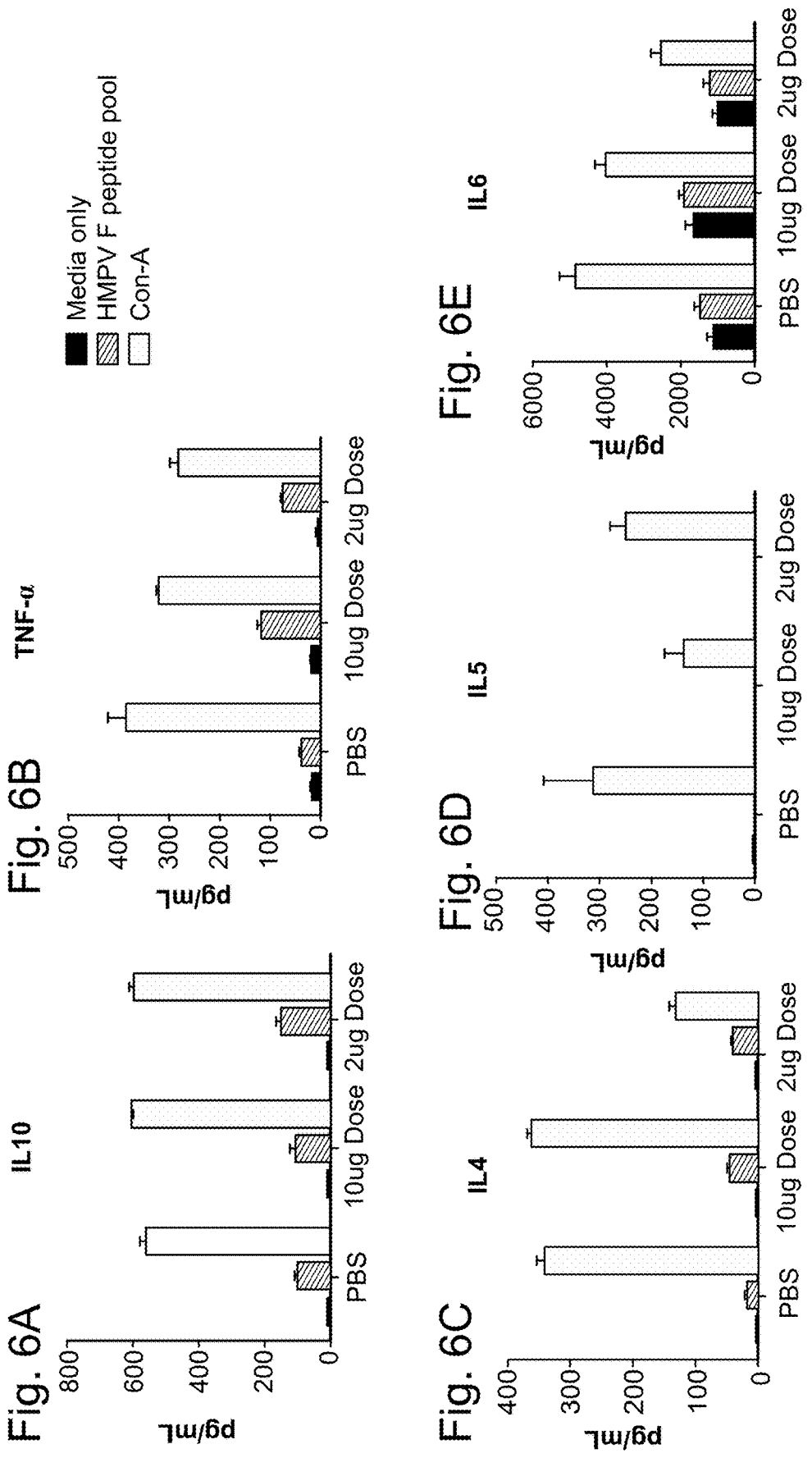


Fig. 5C
IL12
pg/mL
0
50
100
150
200
250
PBS
10ug Dose
2ug Dose


Media only
HMPV F peptide pool
Con-A
Fig. 6A
IL10
pg/mL
0
200
400
600
800
PBS
10ug Dose
2ug Dose
Fig. 6B
TNF-α
pg/mL
0
100
200
300
400
500
PBS
10ug Dose
2ug Dose
Fig. 6C
IL4
pg/mL
0
100
200
300
400
PBS
10ug Dose
2ug Dose
Fig. 6D
IL5
pg/mL
0
100
200
300
400
500
PBS
10ug Dose
2ug Dose
Fig. 6E
IL6
pg/mL
0
2000
4000
6000
PBS
10ug Dose
2ug Dose

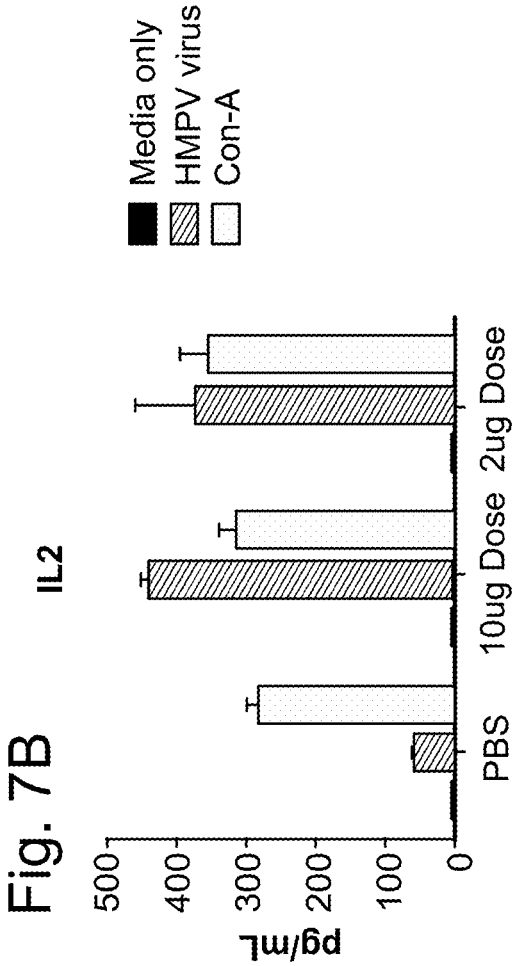


Fig. 7B

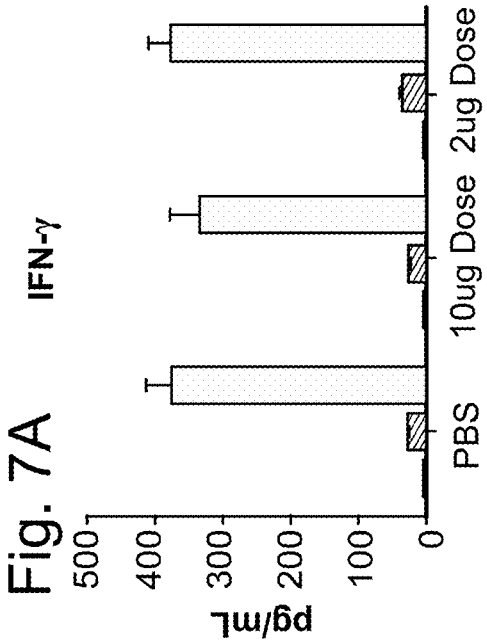


Fig. 7A

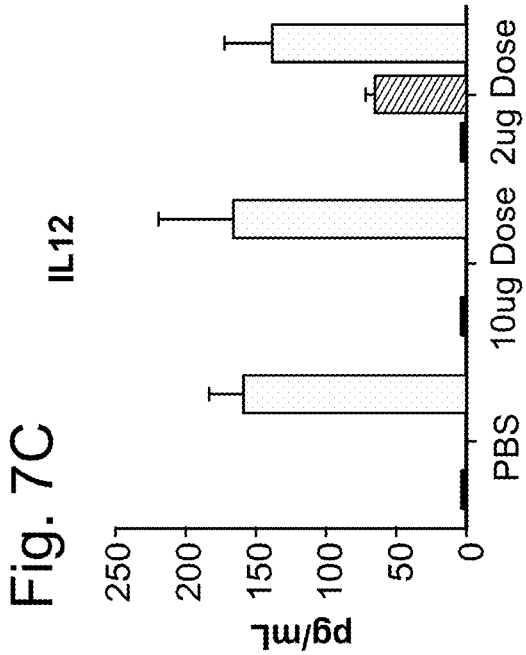


Fig. 7C

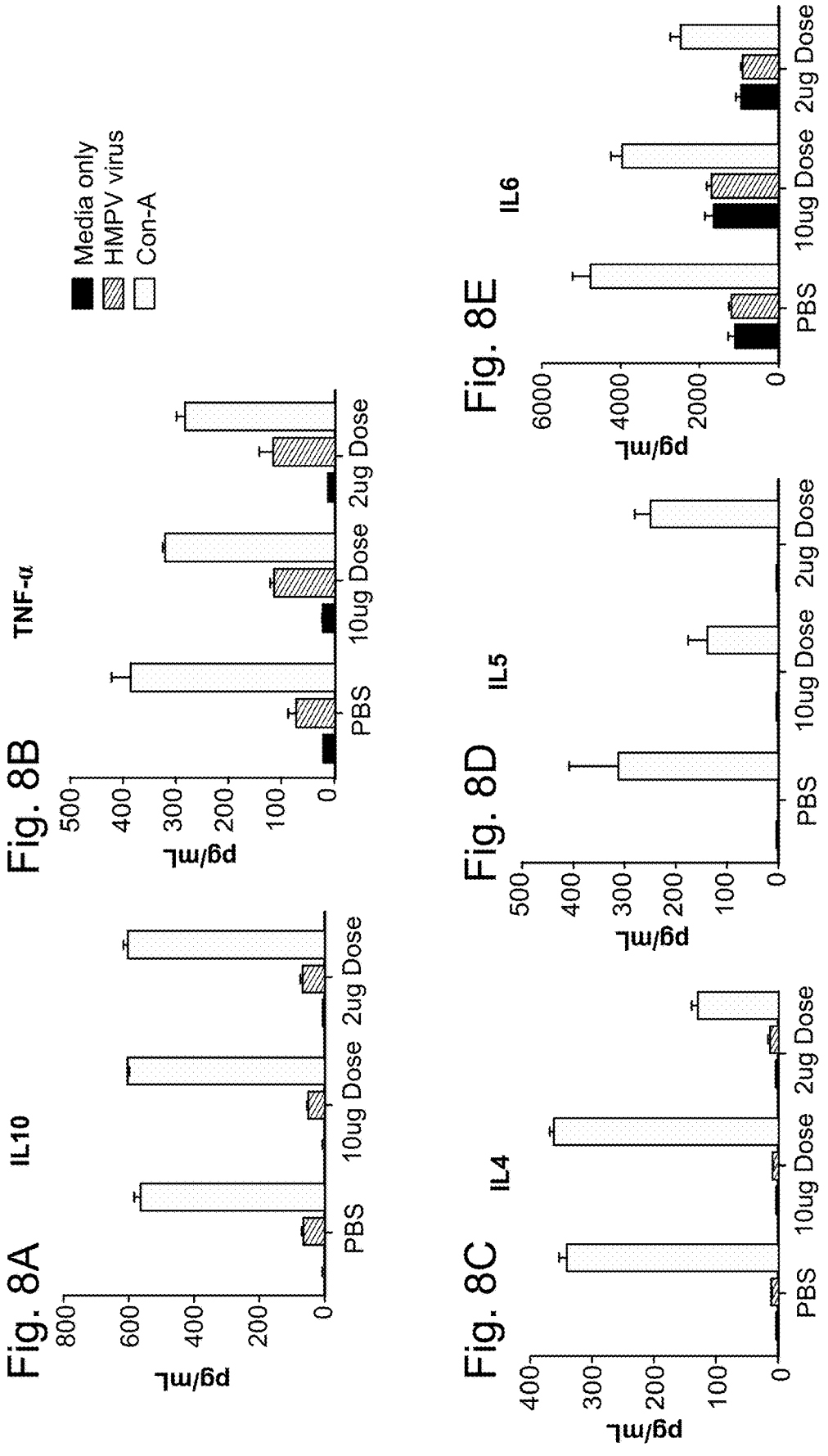


Fig. 8A
IL10
pg/mL
0
200
400
600
800
PBS
10ug Dose
2ug Dose
Fig. 8B
TNF-α
pg/mL
0
100
200
300
400
500
PBS
10ug Dose
2ug Dose
Media only
HMPV virus
Con-A
Fig. 8C
IL4
pg/mL
0
100
200
300
400
PBS
10ug Dose
2ug Dose
Fig. 8D
IL5
pg/mL
0
100
200
300
400
500
PBS
10ug Dose
2ug Dose
Fig. 8E
IL6
pg/mL
0
2000
4000
6000
PBS
10ug Dose
2ug Dose

Fig. 9A

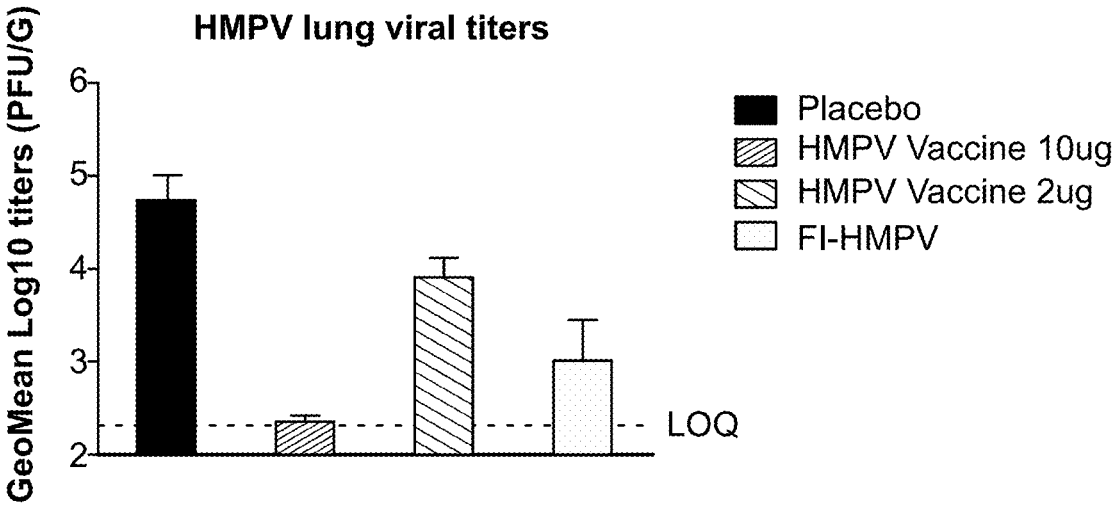

HMPV lung viral titers
GeoMean Log10 titers (PFU/G)
6
5
4
3
2
LOQ
Placebo
HMPV Vaccine 10ug
HMPV Vaccine 2ug
FI-HMPV

Fig. 9B

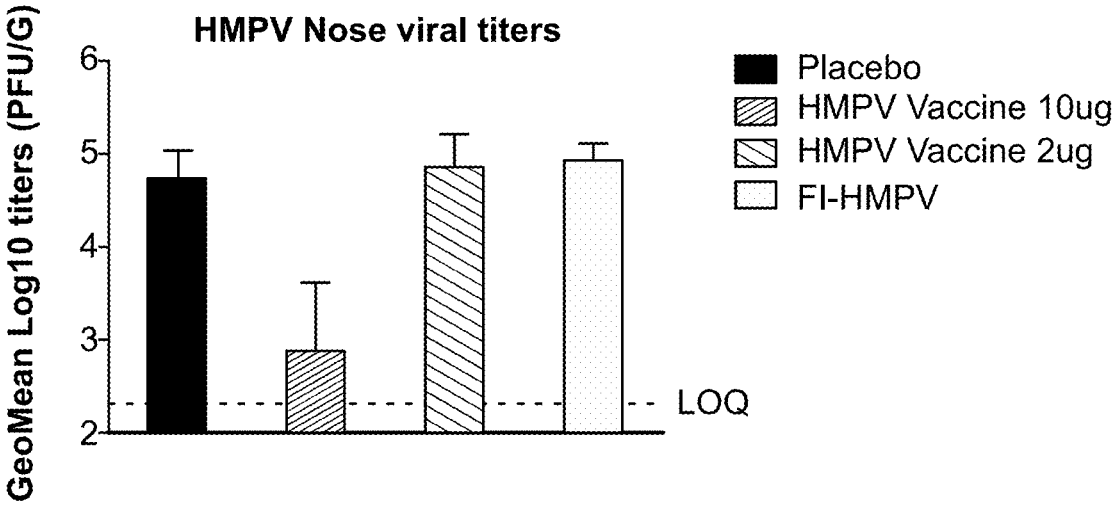

HMPV Nose viral titers
GeoMean Log10 titers (PFU/G)
6
5
4
3
2
LOQ
Placebo
HMPV Vaccine 10ug
HMPV Vaccine 2ug
FI-HMPV

Fig. 10

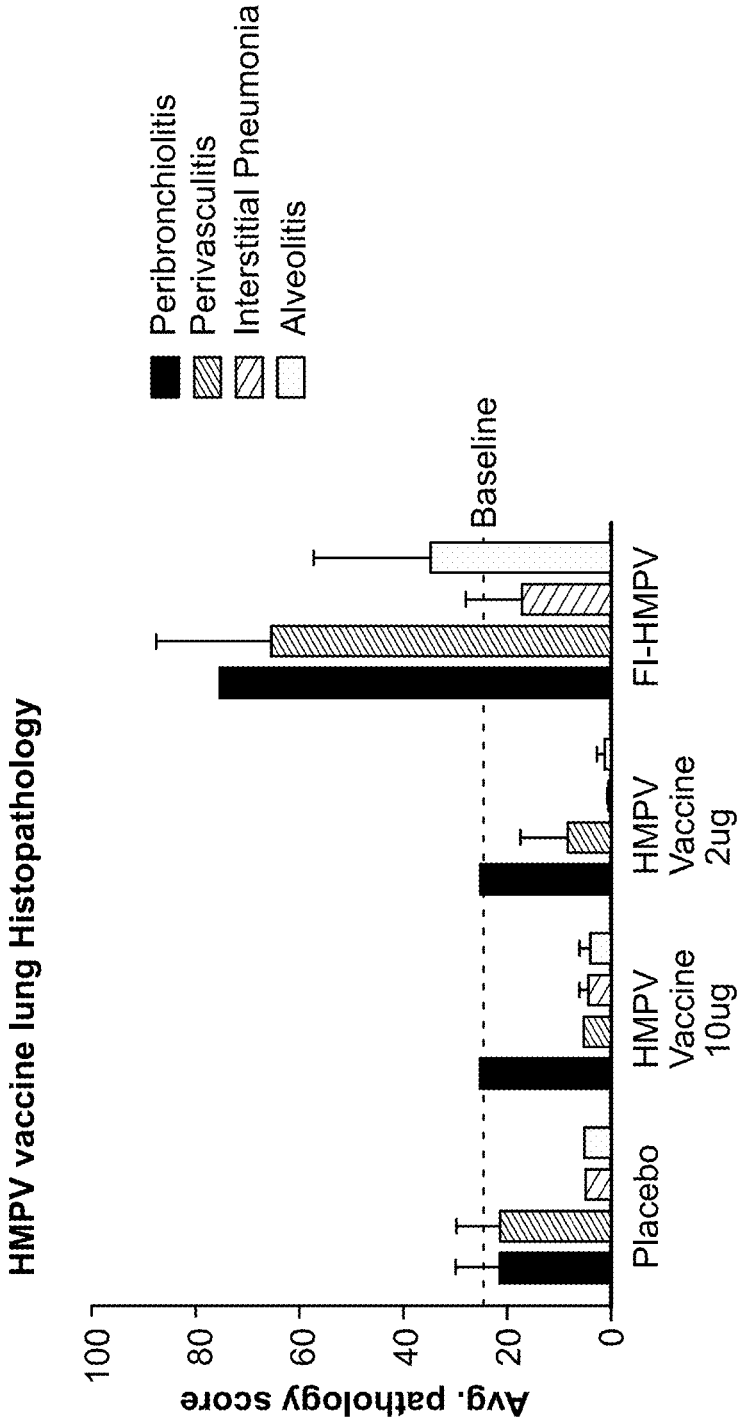
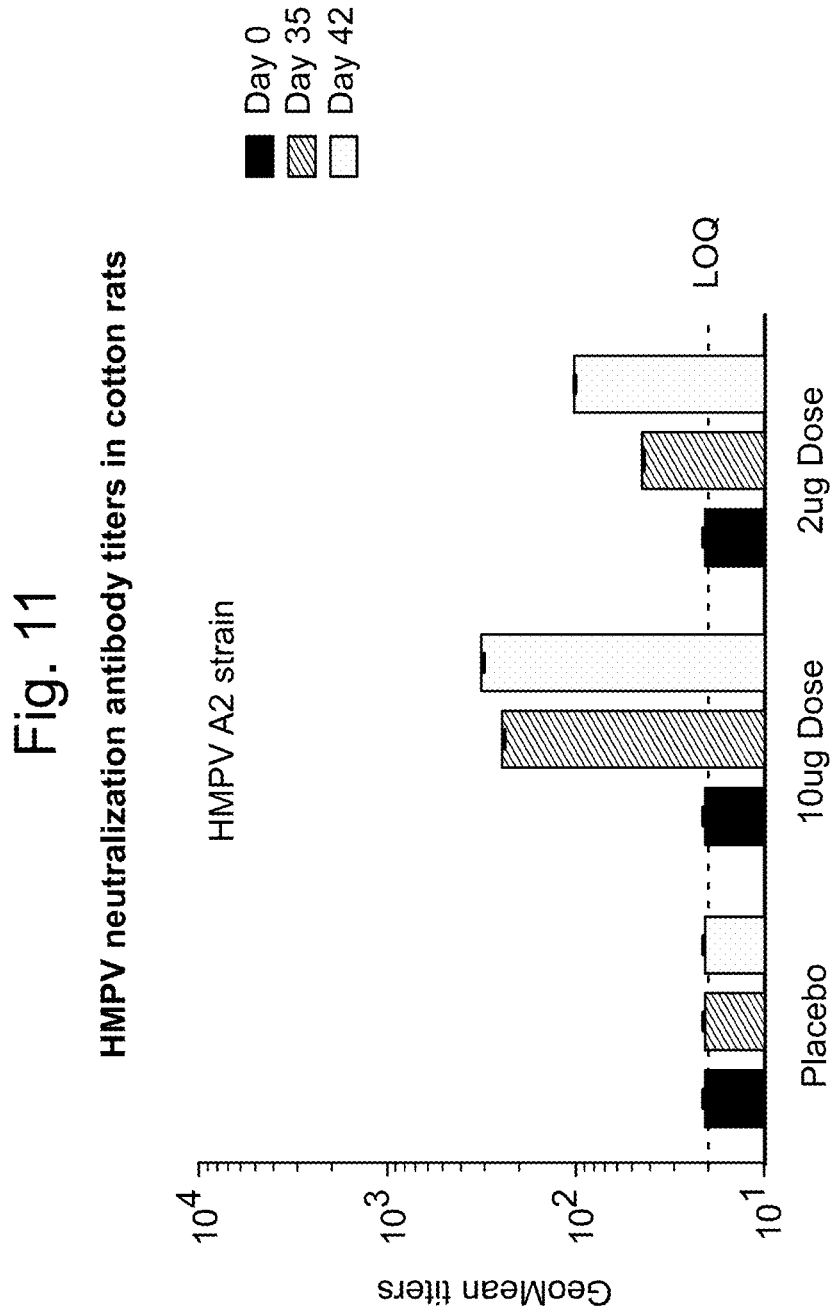

HMPV vaccine lung Histopathology
Peribronchiolitis
Perivasculitis
Interstitial Pneumonia
Alveolitis
Avg. pathology score
100
80
60
40
20
0
Placebo
HMPV Vaccine 10ug
HMPV Vaccine 2ug
FI-HMPV
Baseline

Fig. 11


HMPV neutralization antibody titers in cotton rats
HMPV A2 strain
Day 0
Day 35
Day 42
LOQ
GeoMean titers
10^4
10^3
10^2
10^1
Placebo
10ug Dose
2ug Dose

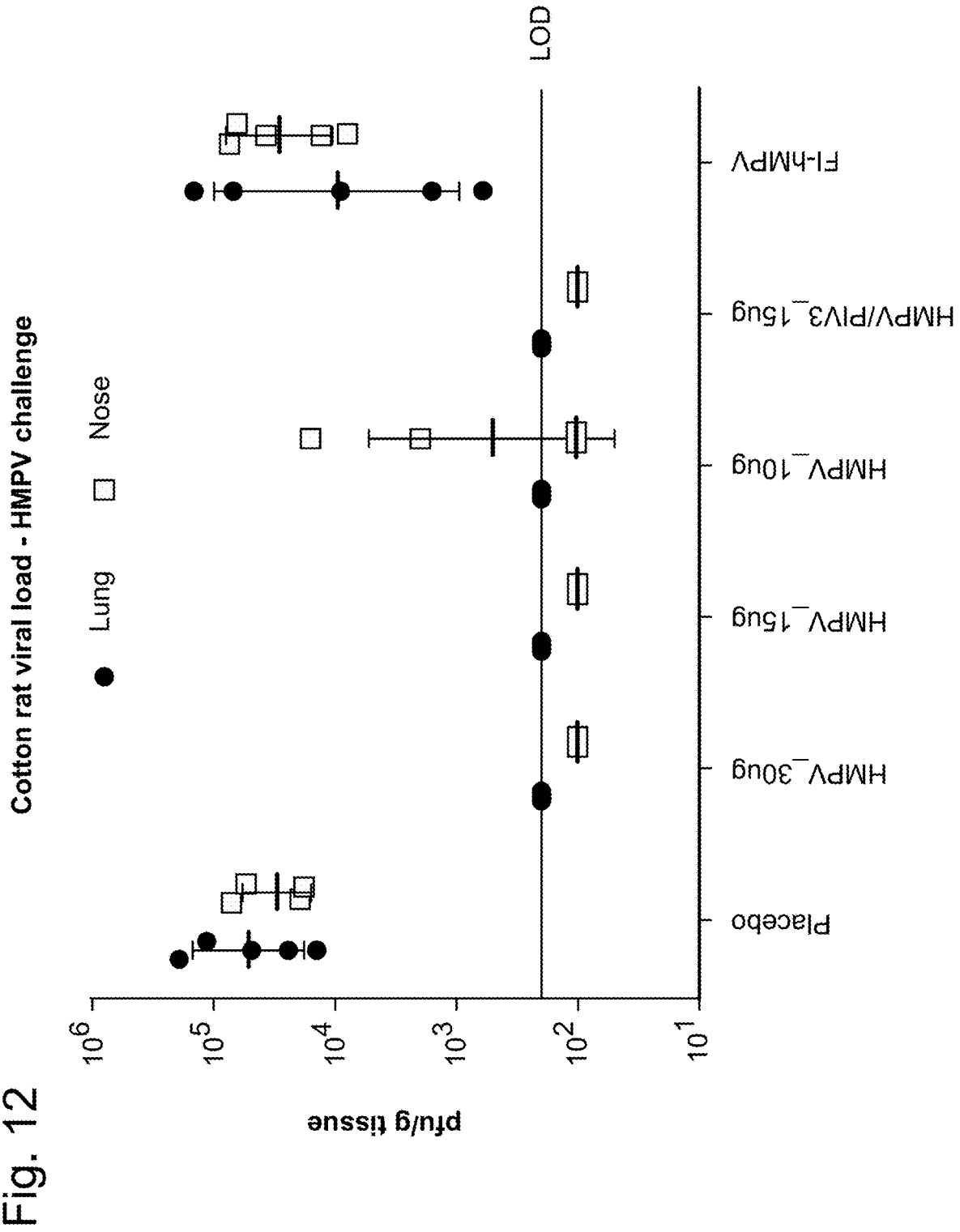

Cotton rat viral load - HMPV challenge
Lung
Nose
LOD
Fl-hMPV
HMPV/PIV3_15ug
HMPV_10ug
HMPV_15ug
HMPV_30ug
Placebo
10^6
10^5
10^4
10^3
10^2
10^1
pfu/g tissue

Fig. 12

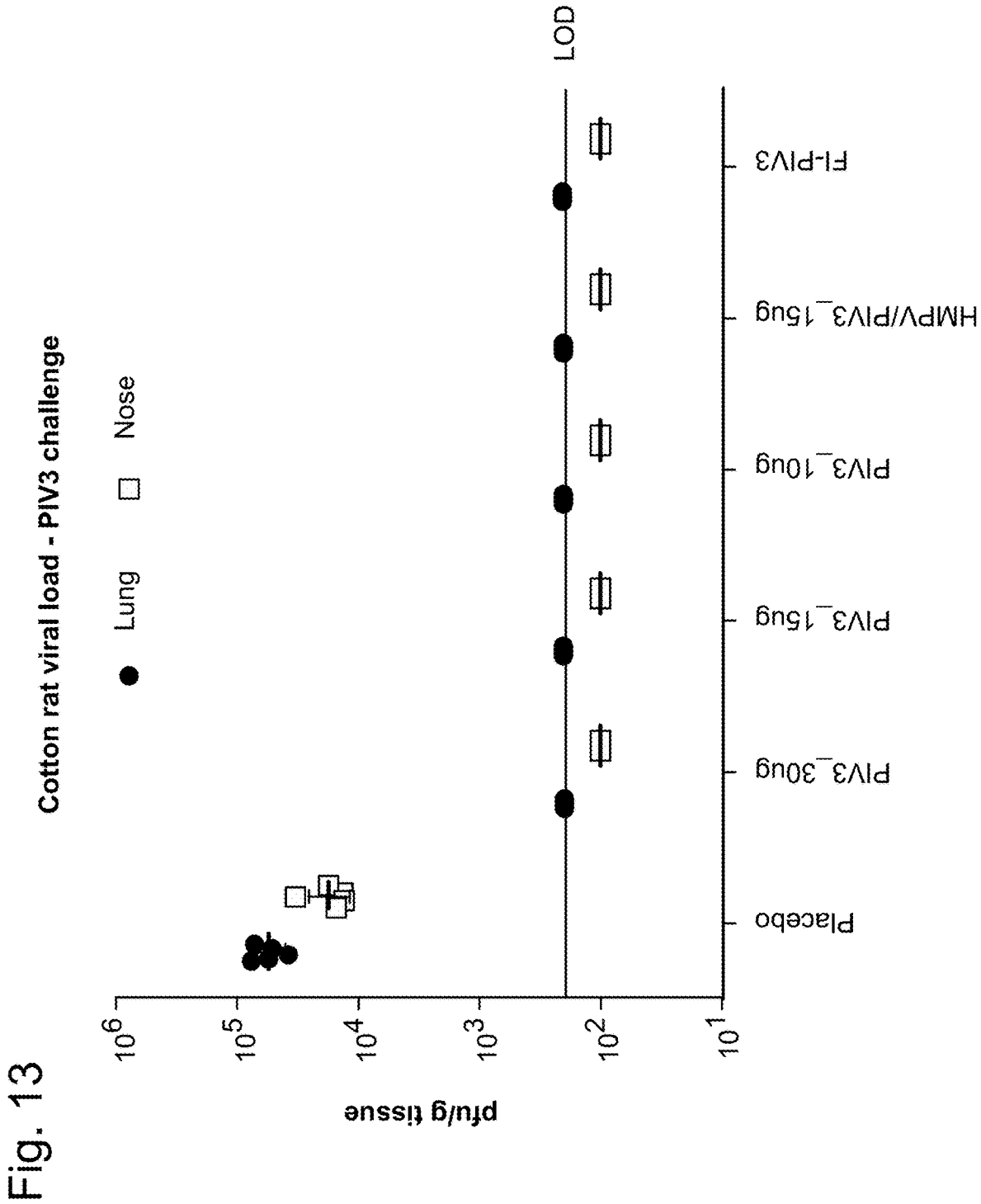

Cotton rat viral load - PIV3 challenge
Lung
Nose
LOD
pfu/g tissue
10^6
10^5
10^4
10^3
10^2
10^1
Placebo
PIV3_30ug
PIV3_15ug
PIV3_10ug
HMPV/PIV3_15ug
FI-PIV3

Fig. 13

Fig. 14

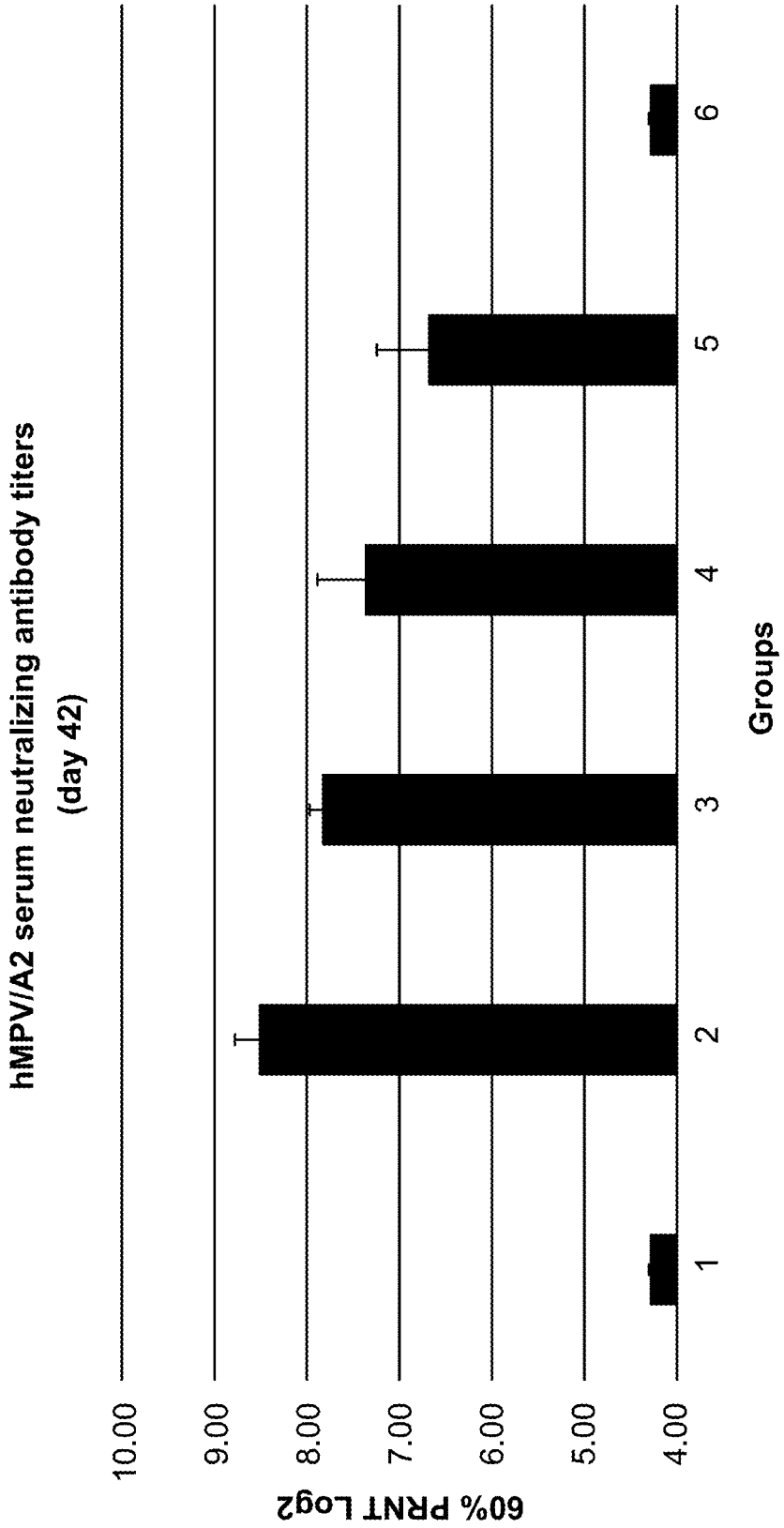

hMPV/A2 serum neutralizing antibody titers
(day 42)
60% PRNT Log2
10.00
9.00
8.00
7.00
6.00
5.00
4.00
1
2
3
4
5
6
Groups

Fig. 15

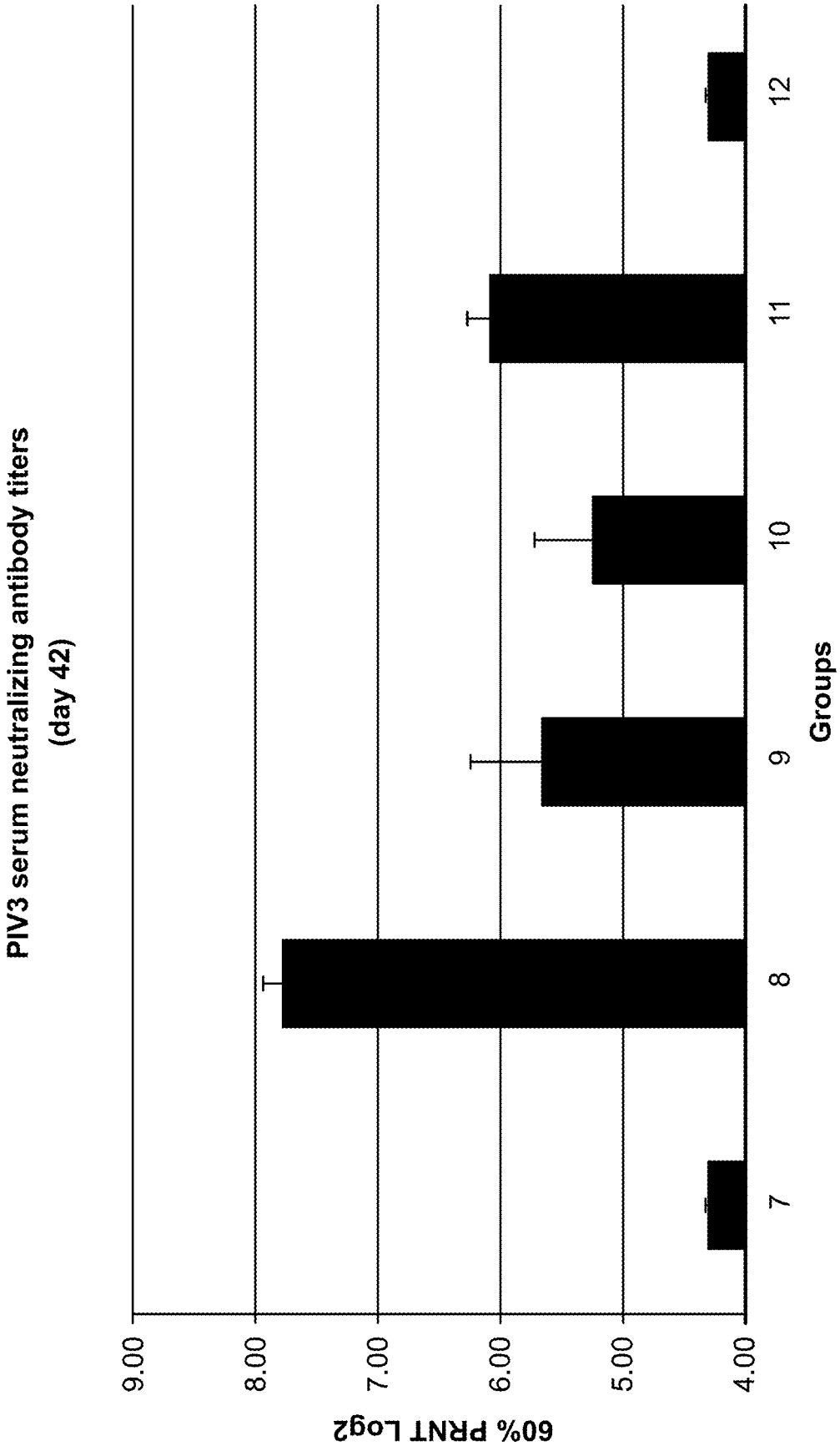

PIV3 serum neutralizing antibody titers
(day 42)
60% PRNT Log2
9.00
8.00
7.00
6.00
5.00
4.00
7
8
9
10
11
12
Groups

Fig. 16

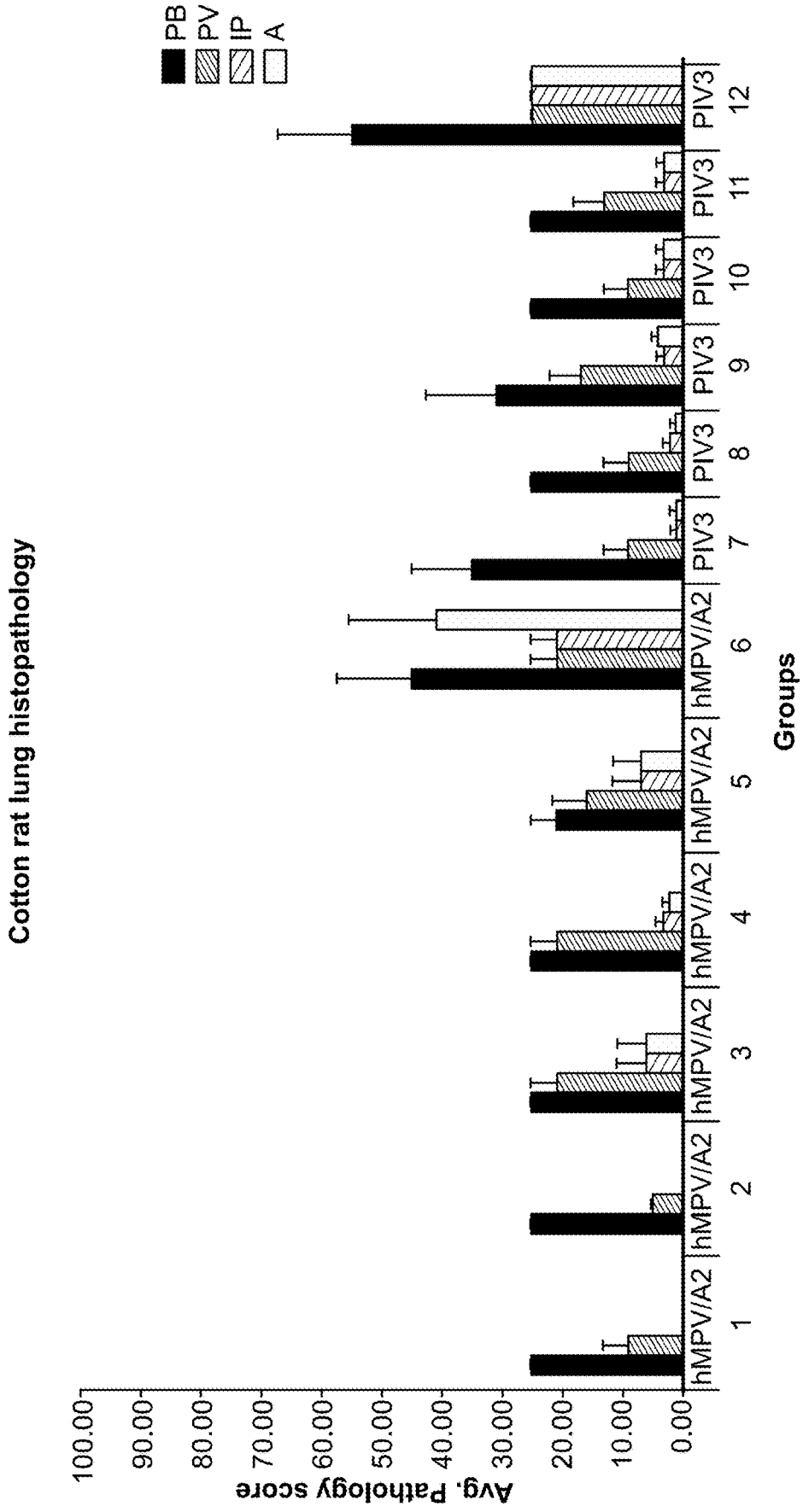

Cotton rat lung histopathology
PB
PV
IP
A
Avg. Pathology score
100.00
90.00
80.00
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
hMPV/A2
hMPV/A2
hMPV/A2
hMPV/A2
hMPV/A2
hMPV/A2
PIV3
PIV3
PIV3
PIV3
PIV3
PIV3
1
2
3
4
5
6
7
8
9
10
11
12
Groups

Fig. 17

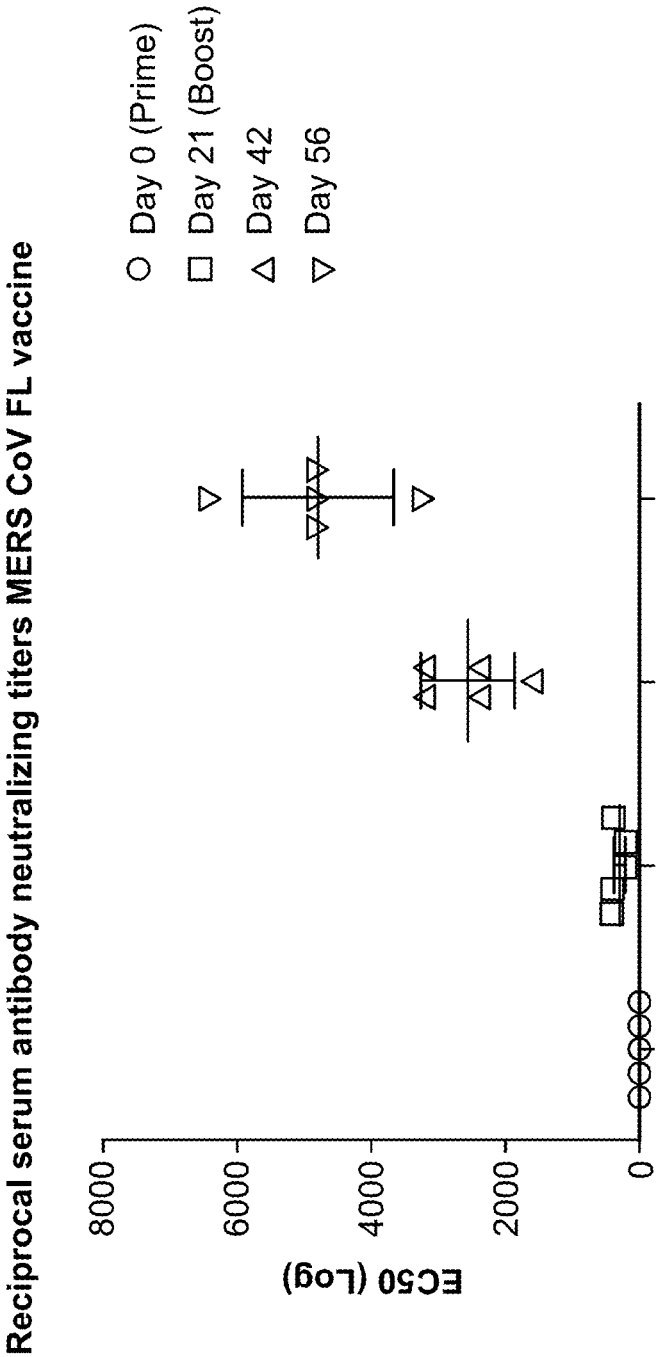

Reciprocal serum antibody neutralizing titers MERS CoV FL vaccine
EC50 (Log)
8000
6000
4000
2000
0
Day 0 (Prime)
Day 21 (Boost)
Day 42
Day 56

Fig. 18

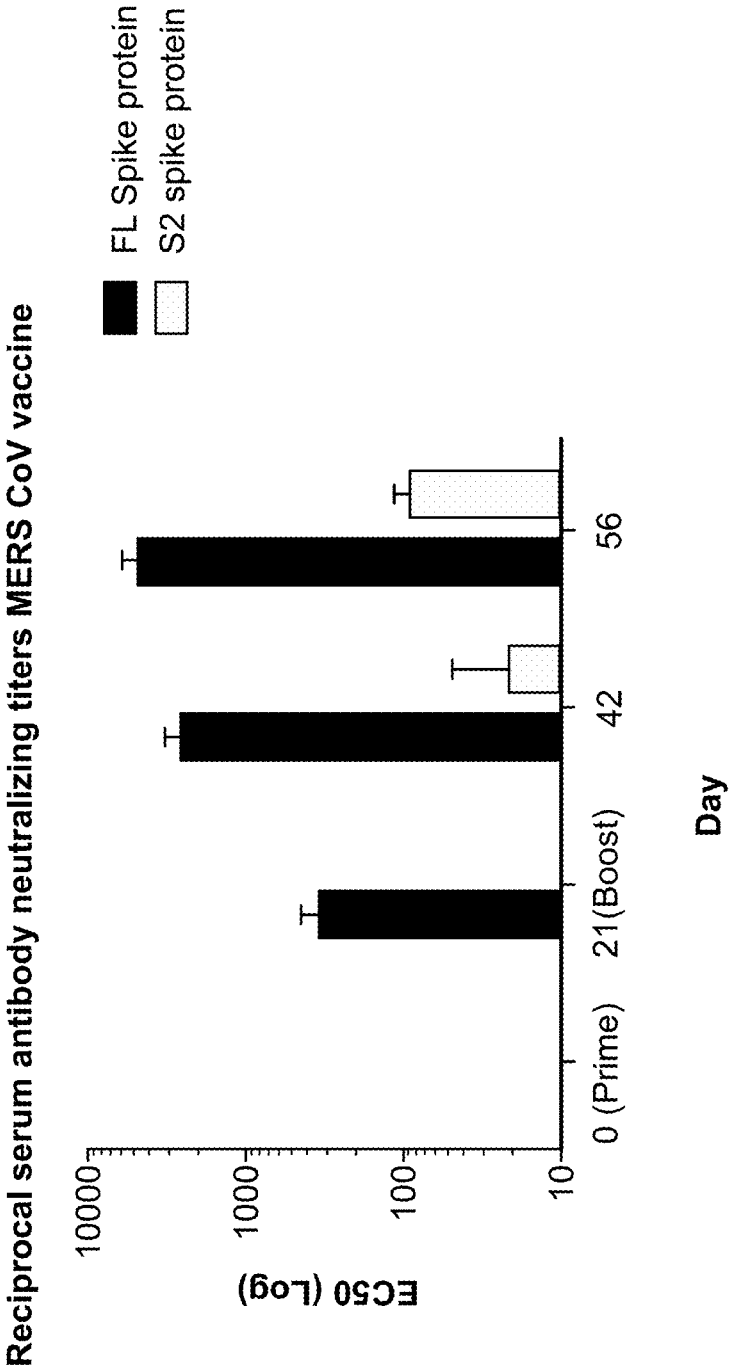

Reciprocal serum antibody neutralizing titers MERS CoV vaccine
FL Spike protein
S2 spike protein
EC50 (Log)
10000
1000
100
10
0 (Prime)
21(Boost)
42
56
Day

Fig. 19A

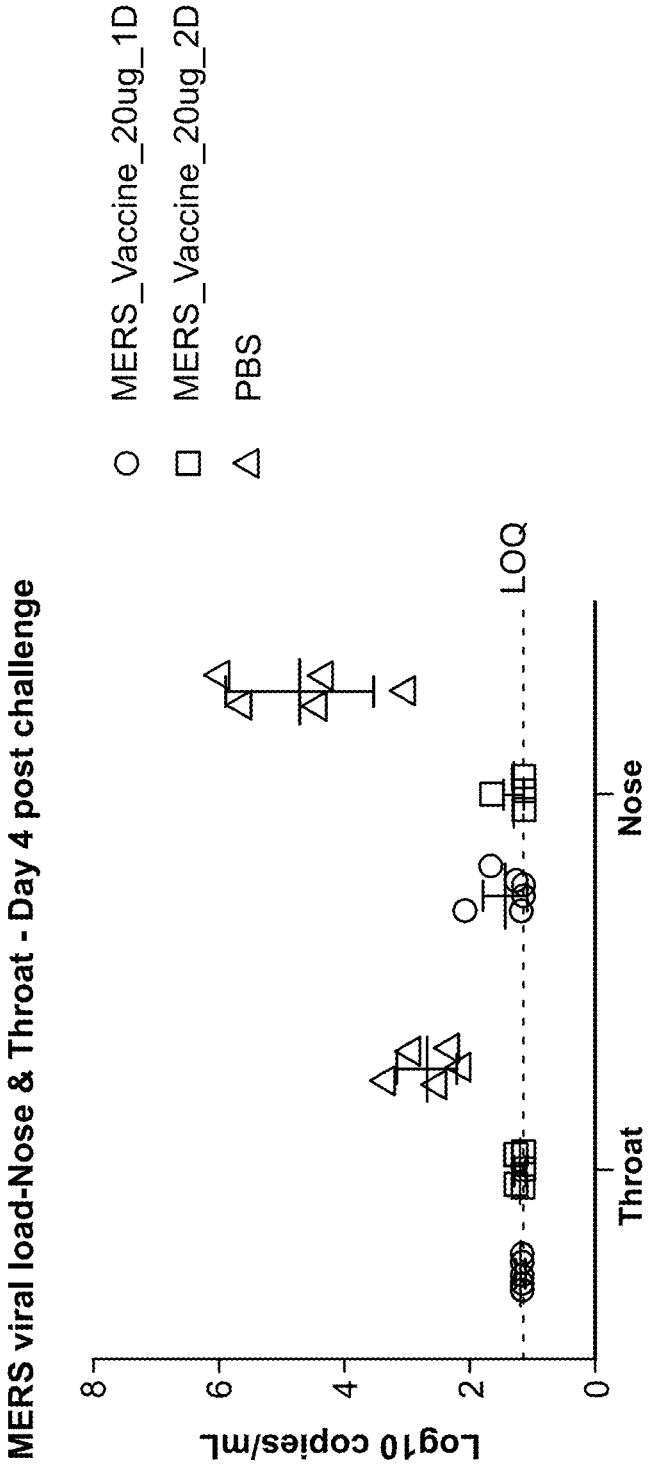

MERS viral load-Nose & Throat - Day 4 post challenge
MERS_Vaccine_20ug_1D
MERS_Vaccine_20ug_2D
PBS
Log10 copies/mL
8
6
4
2
0
LOQ
Nose
Throat

Fig. 19B

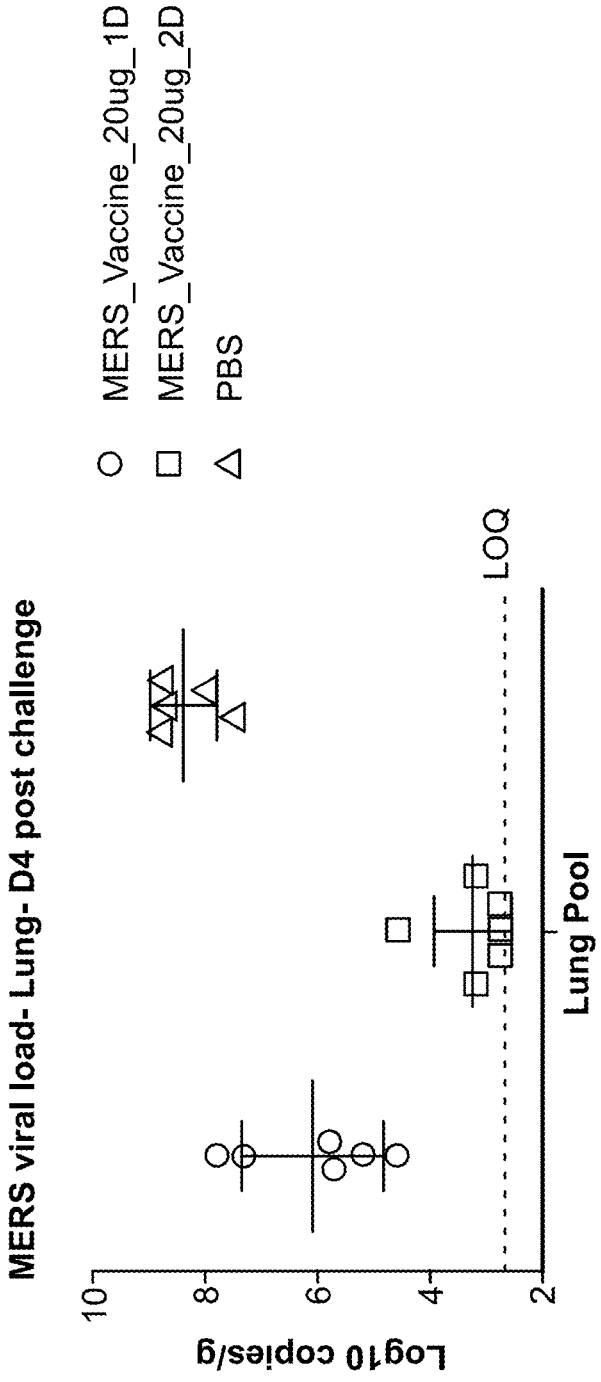

MERS viral load- Lung- D4 post challenge
MERS_Vaccine_20ug_1D
MERS_Vaccine_20ug_2D
PBS
LOQ
Log10 copies/g
10
8
6
4
2
Lung Pool

Fig. 19C

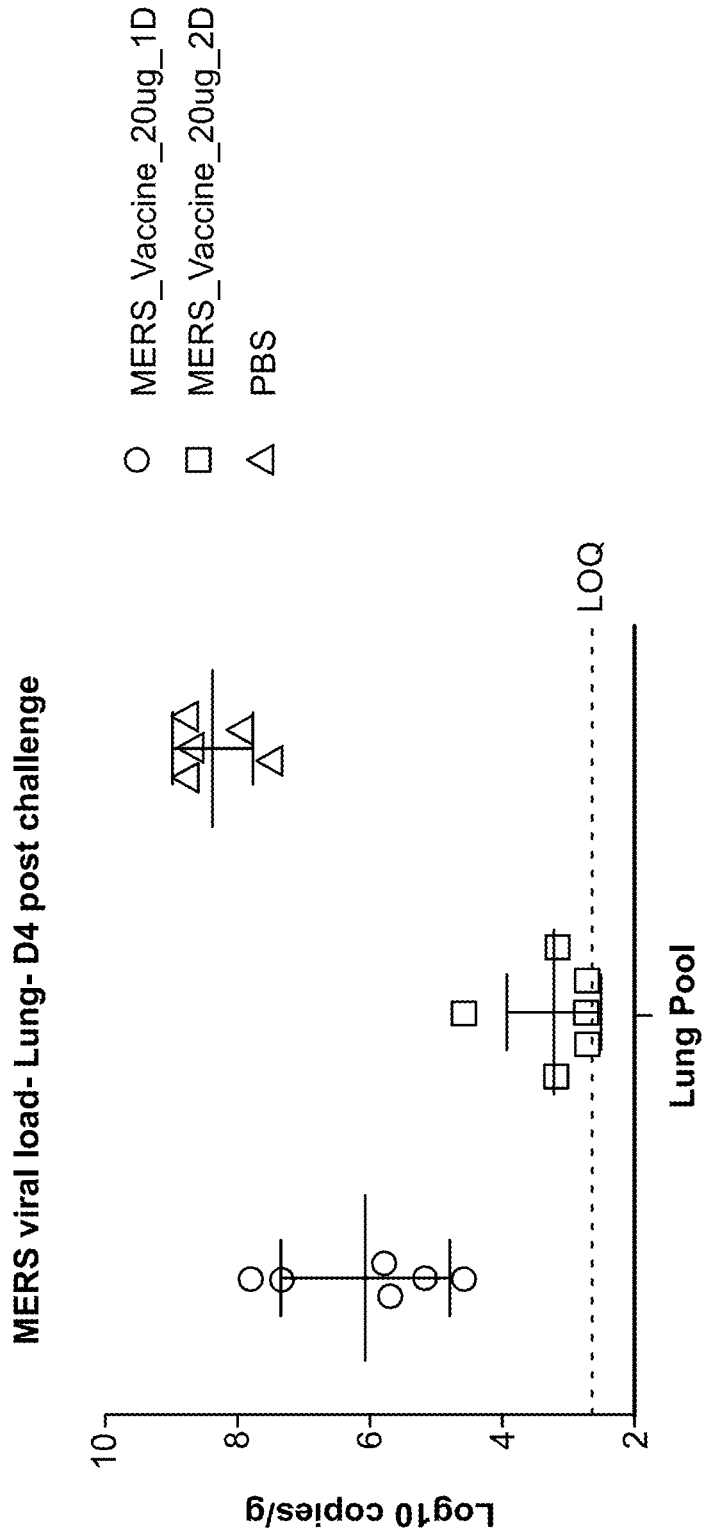

MERS_Vaccine_20ug_1D
MERS_Vaccine_20ug_2D
PBS
MERS viral load- Lung- D4 post challenge
LOQ
Log10 copies/g
10
8
6
4
2
Lung Pool

Fig. 20A

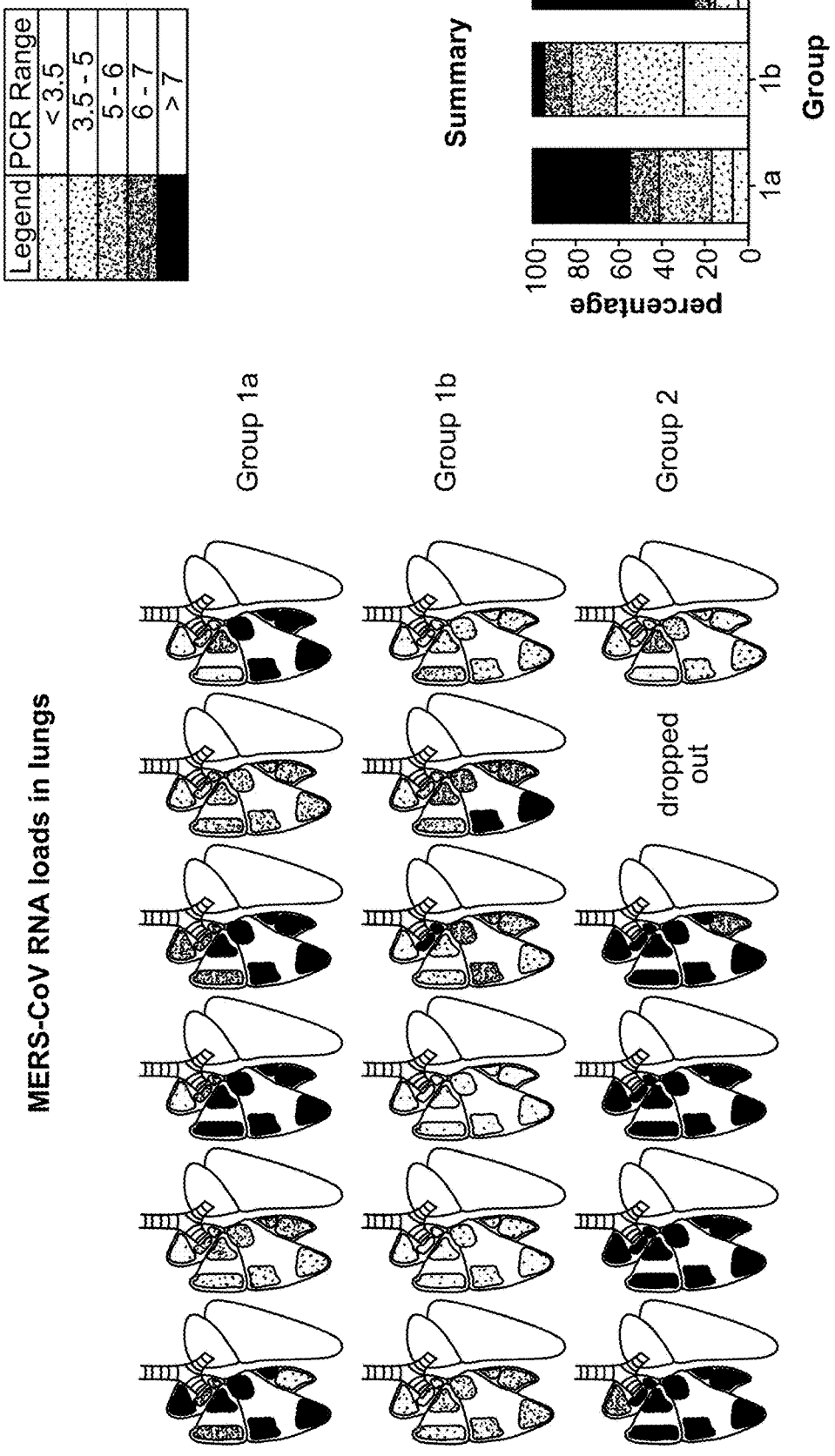

Legend
PCR Range
< 3.5
3.5 - 5
5 - 6
6 - 7
> 7
Summary
percentage
100
80
60
40
20
0
1a
1b
2
Group
MERS-CoV RNA loads in lungs
Group 1a
Group 1b
Group 2
dropped out

Fig. 20B

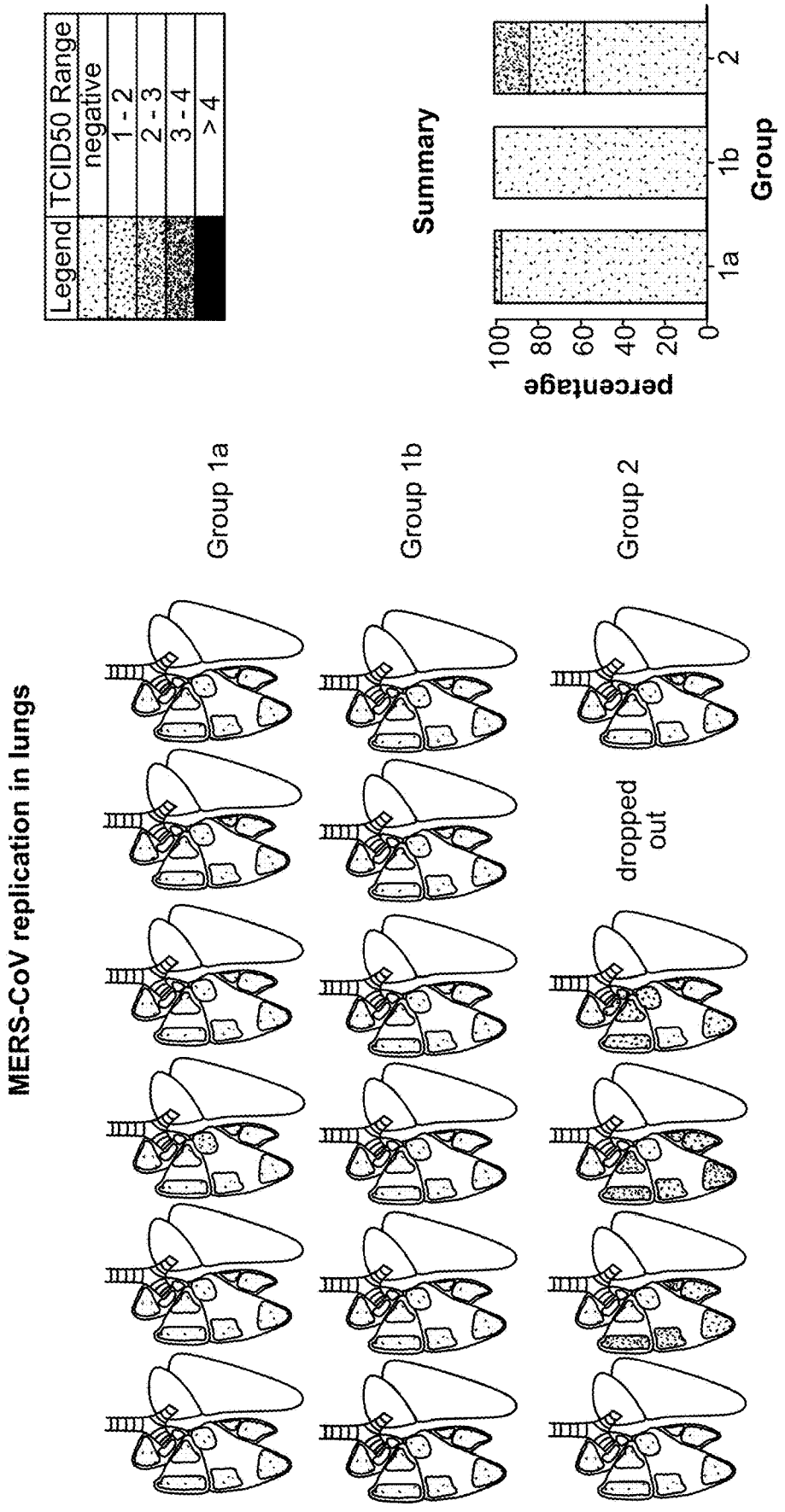
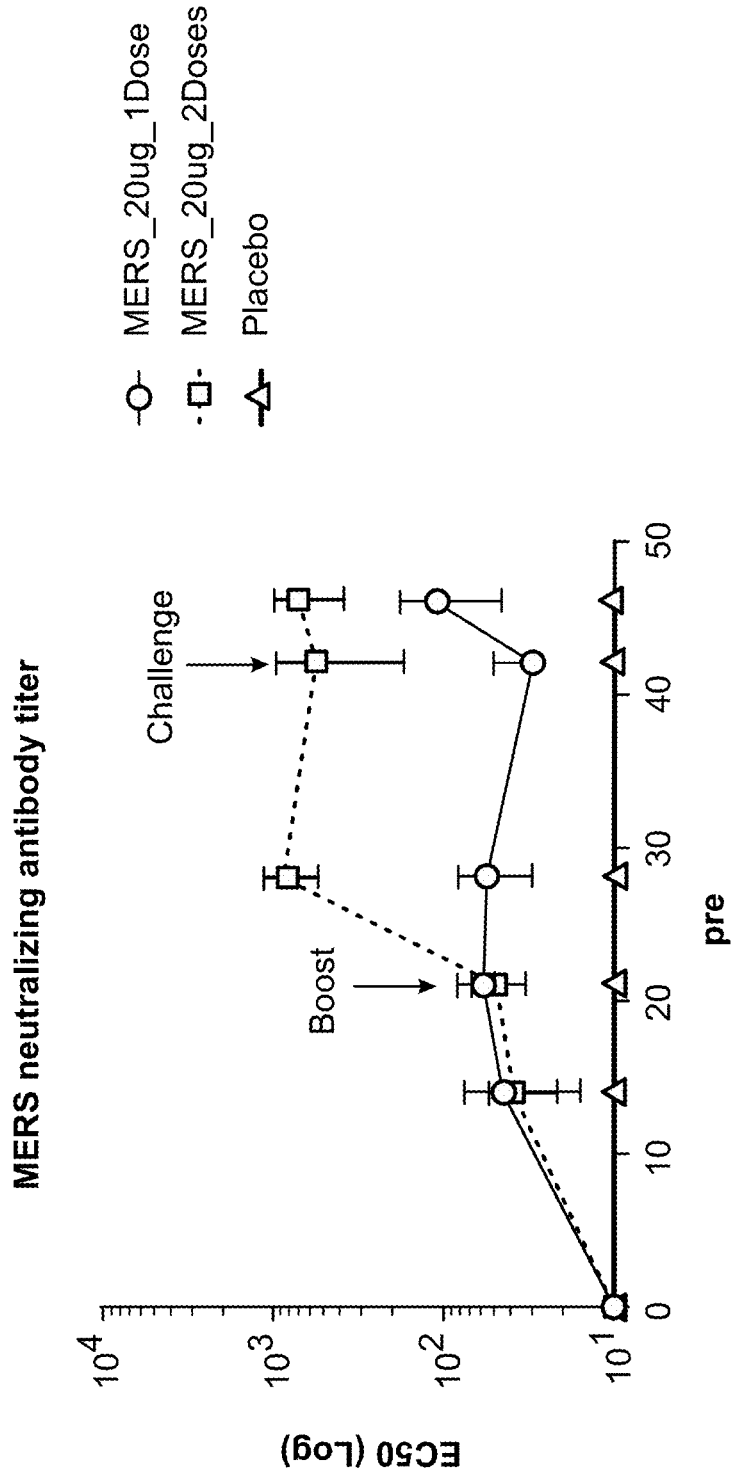

MERS-CoV replication in lungs
Group 1a
Group 1b
Group 2
dropped out
Legend
TCID50 Range
negative
1 - 2
2 - 3
3 - 4
> 4
Summary
percentage
100
80
60
40
20
0
1a
1b
2
Group

Fig. 21


MERS_20ug_1Dose
MERS_20ug_2Doses
Placebo
MERS neutralizing antibody titer
Challenge
Boost
pre
0
10
20
30
40
50
10^1
10^2
10^3
10^4
EC50 (Log)

BETACORONAVIRUS MRNA VACCINE

RELATED APPLICATIONS

This application is a division of U.S. application Ser. No. 16/805,587, filed Feb. 28, 2020, now U.S. Pat. No. 10,702,600, which is a continuation of U.S. application Ser. No. 16/368,270, filed Mar. 28, 2019, now U.S. Pat. No. 10,702,599, which is a continuation of Ser. No. 16/040,981, filed Jul. 20, 2018, now U.S. Pat. No. 10,272,150, which is a continuation of U.S. application Ser. No. 15/674,599, filed Aug. 11, 2017, now U.S. Pat. No. 10,064,934, which is a continuation of International application number PCT/US2016/058327, filed Oct. 21, 2016, which claims the benefit under 35 U.S.C. § 119(e) of U.S. provisional application No. 62/244,802, filed Oct. 22, 2015, U.S. provisional application No. 62/247,297, filed Oct. 28, 2015, U.S. provisional application No. 62/244,946, filed Oct. 22, 2015, U.S. provisional application No. 62/247,362, filed Oct. 28, 2015, U.S. provisional application No. 62/244,813, filed Oct. 22, 2015, U.S. provisional application No. 62/247,394, filed Oct. 28, 2015, U.S. provisional application No. 62/244,837, filed Oct. 22, 2015, U.S. provisional application No. 62/247,483, filed Oct. 28, 2015, and U.S. provisional application No. 62/245,031, filed Oct. 22, 2015, each of which is incorporated by reference herein in its entirety.

BACKGROUND

Respiratory disease is a medical term that encompasses pathological conditions affecting the organs and tissues that make gas exchange possible in higher organisms, and includes conditions of the upper respiratory tract, trachea, bronchi, bronchioles, alveoli, pleura and pleural cavity, and the nerves and muscles of breathing. Respiratory diseases range from mild and self-limiting, such as the common cold, to life-threatening entities like bacterial pneumonia, pulmonary embolism, acute asthma and lung cancer. Respiratory disease is a common and significant cause of illness and death around the world. In the US, approximately 1 billion "common colds" occur each year. Respiratory conditions are among the most frequent reasons for hospital stays among children.

The human *Metapneumovirus* (hMPV) is a negative-sense, single-stranded RNA virus of the genus *Pneumovirinae* and of the family Paramyxoviridae and is closely related to the avian *Metapneumovirus* (AMPV) subgroup C. It was isolated for the first time in 2001 in the Netherlands by using the RAP-PCR (RNA arbitrarily primed PCR) technique for identification of unknown viruses growing in cultured cells. hPMV is second only to RSV as an important cause of viral lower respiratory tract illness (LRI) in young children. The seasonal epidemiology of hMPV appears to be similar to that of RSV, but the incidence of infection and illness appears to be substantially lower.

Parainfluenza virus type 3 (PIV3), like hMPV, is also a negative-sense, single-stranded sense RNA virus of the genus *Pneumovirinae* and of the family Paramyxoviridae and is a major cause of ubiquitous acute respiratory infections of infancy and early childhood. Its incidence peaks around 4-12 months of age, and the virus is responsible for 3-10% of hospitalizations, mainly for bronchiolitis and pneumonia. PIV3 can be fatal, and in some instances is associated with neurologic diseases, such as febrile seizures. It can also result in airway remodeling, a significant cause of morbidity. In developing regions of the world, infants and young children are at the highest risk of mortality, either from primary PIV3 viral infection or a secondary consequences, such as bacterial infections. Human parainfluenza viruses (hPIV) types 1, 2 and 3 (hPIV1, hPIV2 and hPIV3, respectively), also like hMPV, are second only to RSV as important causes of viral LRI in young children.

RSV, too, is a negative-sense, single-stranded RNA virus of the genus *Pneumovirinae* and of the family Paramyxoviridae. Symptoms in adults typically resemble a sinus infection or the common cold, although the infection may be asymptomatic. In older adults (e.g., >60 years), RSV infection may progress to bronchiolitis or pneumonia. Symptoms in children are often more severe, including bronchiolitis and pneumonia. It is estimated that in the United States, most children are infected with RSV by the age of three. The RSV virion consists of an internal nucleocapsid comprised of the viral RNA bound to nucleoprotein (N), phosphoprotein (P), and large polymerase protein (L). The nucleocapsid is surrounded by matrix protein (M) and is encapsulated by a lipid bilayer into which the viral fusion (F) and attachment (G) proteins as well as the small hydrophobic protein (SH) are incorporated. The viral genome also encodes two nonstructural proteins (NS1 and NS2), which inhibit type I interferon activity as well as the M-2 protein.

The continuing health problems associated with hMPV, PIV3 and RSV are of concern internationally, reinforcing the importance of developing effective and safe vaccine candidates against these virus.

Despite decades of research, no vaccines currently exist (Sato and Wright, *Pediatr. Infect. Dis. J.* 2008; 27(10 Suppl): S123-5). Recombinant technology, however, has been used to target the formation of vaccines for hPIV-1, 2 and 3 serotypes, for example, and has taken the form of several live-attenuated intranasal vaccines. Two vaccines in particular were found to be immunogenic and well tolerated against hPIV-3 in phase I trials. hPIV1 and hPIV2 vaccine candidates remain less advanced (Durbin and Karron, Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 2003; 37(12):1668-77).

Measles virus (MeV), like hMPV, PIV3 and RSV, is a negative-sense, single-stranded RNA virus that is the cause of measles, an infection of the respiratory system. MeV is of the genus *Morbillivirus* within the family Paramyxoviridae. Humans are the natural hosts of the virus; no animal reservoirs are known to exist. Symptoms of measles include fever, cough, runny nose, red eyes and a generalized, maculopapular, erythematous rash. The virus is highly contagious and is spread by coughing

In additional to hMPV, PIV, RSV and MeV, Betacoronaviruses are known to cause respiratory illnesses. Betacoronaviruses (BetaCoVs) are one of four genera of coronaviruses of the subfamily Coronavirinae in the family Coronaviridae, of the order Nidovirales. They are enveloped, positive-sense, single-stranded RNA viruses of zoonotic origin. The coronavirus genera are each composed of varying viral lineages, with the *Betacoronavirus* genus containing four such lineages. The BetaCoVs of the greatest clinical importance concerning humans are OC43 and HKU1 of the A lineage, SARS-CoV of the B lineage, and MERS-CoV of the C lineage. MERS-CoV is the first *Betacoronavirus* belonging to lineage C that is known to infect humans.

The Middle East respiratory syndrome coronavirus (MERS-CoV), or EMC/2012 (HCoV-EMC/2012), initially referred to as novel coronavirus 2012 or simply novel coronavirus, was first reported in 2012 after genome sequencing of a virus isolated from sputum samples from a person who fell ill during a 2012 outbreak of a new flu. As

of July 2015, MERS-CoV cases have been reported in over 21 countries. The outbreaks of MERS-CoV have raised serious concerns world-wide, reinforcing the importance of developing effective and safe vaccine candidates against MERS-CoV.

Severe acute respiratory syndrome (SARS) emerged in China in 2002 and spread to other countries before brought under control. Because of a concern for reemergence or a deliberate release of the SARS coronavirus, vaccine development was initiated.

Deoxyribonucleic acid (DNA) vaccination is one technique used to stimulate humoral and cellular immune responses to foreign antigens, such as hMPV antigens and/or PIV antigens and/or RSV antigens. The direct injection of genetically engineered DNA (e.g., naked plasmid DNA) into a living host results in a small number of its cells directly producing an antigen, resulting in a protective immunological response. With this technique, however, comes potential problems, including the possibility of insertional mutagenesis, which could lead to the activation of oncogenes or the inhibition of tumor suppressor genes.

SUMMARY

Provided herein are ribonucleic acid (RNA) vaccines that build on the knowledge that RNA (e.g., messenger RNA (mRNA)) can safely direct the body's cellular machinery to produce nearly any protein of interest, from native proteins to antibodies and other entirely novel protein constructs that can have therapeutic activity inside and outside of cells. The RNA (e.g., mRNA) vaccines of the present disclosure may be used to induce a balanced immune response against hMPV, PIV, RSV, MeV, and/or BetaCoV (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1), or any combination of two or more of the foregoing viruses, comprising both cellular and humoral immunity, without risking the possibility of insertional mutagenesis, for example. hMPV, PIV, RSV, MeV, BetaCoV (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1) and combinations thereof are referred to herein as "respiratory viruses." Thus, the term "respiratory virus RNA vaccines" encompasses hMPV RNA vaccines, PIV RNA vaccines, RSV RNA vaccines, MeV RNA vaccines, BetaCoV RNA vaccines, and any combination of two or more of hMPV RNA vaccines, PIV RNA vaccines, RSV RNA vaccines, MeV RNA vaccines, and BetaCoV RNA vaccines.

The RNA (e.g., mRNA) vaccines may be utilized in various settings depending on the prevalence of the infection or the degree or level of unmet medical need. The RNA (e.g. mRNA) vaccines may be utilized to treat and/or prevent a hMPV, PIV, RSV, MeV, a BetaCoV (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH, HCoV-HKU1), or any combination of two or more of the foregoing viruses, of various genotypes, strains, and isolates. The RNA (e.g., mRNA) vaccines have superior properties in that they produce much larger antibody titers and produce responses earlier than commercially available anti-viral therapeutic treatments. While not wishing to be bound by theory, it is believed that the RNA (e.g., mRNA) vaccines, as mRNA polynucleotides, are better designed to produce the appropriate protein conformation upon translation as the RNA (e.g., mRNA) vaccines co-opt natural cellular machinery. Unlike traditional vaccines, which are manufactured ex vivo and may trigger unwanted cellular responses, RNA (e.g., mRNA) vaccines are presented to the cellular system in a more native fashion.

In some aspects the invention is a respiratory virus vaccine, comprising at least one RNA polynucleotide having an open reading frame encoding at least one respiratory virus antigenic polypeptide, formulated in a cationic lipid nanoparticle.

Surprisingly, in some aspects it has also been shown that efficacy of mRNA vaccines can be significantly enhanced when combined with a flagellin adjuvant, in particular, when one or more antigen-encoding mRNAs is combined with an mRNA encoding flagellin.

RNA (e.g., mRNA) vaccines combined with the flagellin adjuvant (e.g., mRNA-encoded flagellin adjuvant) have superior properties in that they may produce much larger antibody titers and produce responses earlier than commercially available vaccine formulations. While not wishing to be bound by theory, it is believed that the RNA (e.g., mRNA) vaccines, for example, as mRNA polynucleotides, are better designed to produce the appropriate protein conformation upon translation, for both the antigen and the adjuvant, as the RNA (e.g., mRNA) vaccines co-opt natural cellular machinery. Unlike traditional vaccines, which are manufactured ex vivo and may trigger unwanted cellular responses, RNA (e.g., mRNA) vaccines are presented to the cellular system in a more native fashion.

Some embodiments of the present disclosure provide RNA (e.g., mRNA) vaccines that include at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one antigenic polypeptide or an immunogenic fragment thereof (e.g., an immunogenic fragment capable of inducing an immune response to the antigenic polypeptide) and at least one RNA (e.g., mRNA polynucleotide) having an open reading frame encoding a flagellin adjuvant.

In some embodiments, at least one flagellin polypeptide (e.g., encoded flagellin polypeptide) is a flagellin protein. In some embodiments, at least one flagellin polypeptide (e.g., encoded flagellin polypeptide) is an immunogenic flagellin fragment. In some embodiments, at least one flagellin polypeptide and at least one antigenic polypeptide are encoded by a single RNA (e.g., mRNA) polynucleotide. In other embodiments, at least one flagellin polypeptide and at least one antigenic polypeptide are each encoded by a different RNA polynucleotide.

In some embodiments at least one flagellin polypeptide has at least 80%, at least 85%, at least 90%, or at least 95% identity to a flagellin polypeptide having a sequence identified by any one of SEQ ID NO: 54-56.

Provided herein, in some embodiments, is a ribonucleic acid (RNA) (e.g., mRNA) vaccine, comprising at least one (e.g., at least 2, 3, 4 or 5) RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one (e.g., at least 2, 3, 4 or 5) hMPV, PIV, RSV, MeV, or a BetaCoV (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH, HCoV-HKU1) antigenic polypeptide, or any combination of two or more of the foregoing antigenic polypeptides. Herein, use of the term "antigenic polypeptide" encompasses immunogenic fragments of the antigenic polypeptide (an immunogenic fragment that is induces (or is capable of inducing) an immune response to hMPV, PIV, RSV, MeV, or a BetaCoV), unless otherwise stated.

Also provided herein, in some embodiments, is a RNA (e.g., mRNA) vaccine comprising at least one (e.g., at least 2, 3, 4 or 5) RNA polynucleotide having an open reading frame encoding at least one (e.g., at least 2, 3, 4 or 5) hMPV,

PIV, RSV, MeV, and/or a BetaCoV (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH, HCoV-HKU1) antigenic polypeptide or an immunogenic fragment thereof, linked to a signal peptide.

Further provided herein, in some embodiments, is a nucleic acid (e.g., DNA) encoding at least one (e.g., at least 2, 3, 4 or 5) hMPV, PIV, RSV, MeV, and/or a BetaCoV (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH, HCoV-HKU1) RNA (e.g., mRNA) polynucleotide.

Further still, provided herein, in some embodiments, is a method of inducing an immune response in a subject, the method comprising administering to the subject a vaccine comprising at least one (e.g., at least 2, 3, 4 or 5) RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one (e.g., at least 2, 3, 4 or 5) hMPV, PIV, RSV, MeV, and/or a BetaCoV (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH, HCoV-HKU1) antigenic polypeptide, or any combination of two or more of the foregoing antigenic polypeptides.

hMPV/PIV3/RSV

In some embodiments, a RNA (e.g., mRNA) vaccine comprises at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one hMPV, PIV3 or RSV antigenic polypeptide. In some embodiments, at least one antigenic polypeptide is a hMPV, PIV3 or RSV polyprotein. In some embodiments, at least one antigenic polypeptide is major surface glycoprotein G or an immunogenic fragment thereof. In some embodiments, at least one antigenic polypeptide is Fusion (F) glycoprotein (e.g., Fusion glycoprotein F0, F1 or F2) or an immunogenic fragment thereof. In some embodiments, at least one antigenic polypeptide is major surface glycoprotein G or an immunogenic fragment thereof and F glycoprotein or an immunogenic fragment thereof. In some embodiments, the antigenic polypeptide is nucleoprotein (N) or an immunogenic fragment thereof, phosphoprotein (P) or an immunogenic fragment thereof, large polymerase protein (L) or an immunogenic fragment thereof, matrix protein (M) or an immunogenic fragment thereof, small hydrophobic protein (SH) or an immunogenic fragment thereof nonstructural protein 1 (NS1) or an immunogenic fragment thereof, or nonstructural protein 2 (NS2) and an immunogenic fragment thereof.

In some embodiments, at least one hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 (Table 3; see also amino acid sequences of Table 4). In some embodiments, the amino acid sequence of the hMPV antigenic polypeptide is, or is a fragment of, or is a homolog or variant having at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) identity to, the amino acid sequence identified by any one of SEQ ID NO: 5-8 (Table 3; see also amino acid sequences of Table 4).

In some embodiments, at least one hMPV antigenic polypeptide is encoded by a nucleic acid sequence identified by any one of SEQ ID NO: 1-4 (Table 2).

In some embodiments, at least one hMPV RNA (e.g., mRNA) polynucleotide is encoded by a nucleic acid sequence, or a fragment of a nucleotide sequence, identified by any one of SEQ ID NO: 1-4 (Table 2). In some embodiments, at least one hMPV RNA (e.g., mRNA) polynucleotide comprises a nucleic acid sequence, or a fragment of a nucleotide sequence, identified by any one of SEQ ID NO: 57-60 (Table 2).

In some embodiments, at least one antigenic polypeptide is obtained from hMPV strain CAN98-75 (CAN75) or the hMPV strain CAN97-83 (CAN83).

In some embodiments, at least one PIV3 antigenic polypeptide comprises hemagglutinin-neuraminidase, Fusion (F) glycoprotein, matrix protein (M), nucleocapsid protein (N), viral replicase (L), non-structural V protein, or an immunogenic fragment thereof.

In some embodiments, at least one PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 (Table 6; see also amino acid sequences of Table 7). In some embodiments, the amino acid sequence of the PIV3 antigenic polypeptide is, or is a fragment of, or is a homolog or variant having at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) identity to, the amino acid sequence identified by any one of SEQ ID NO: 12-13 (Table 6; see also amino acid sequences of Table 7).

In some embodiments, at least one PIV3 antigenic polypeptide is encoded by a nucleic acid sequence identified by any one of SEQ ID NO: 9-12 (Table 5; see also nucleic acid sequences of Table 7).

In some embodiments, at least one PIV3 RNA (e.g., mRNA) polynucleotide is encoded by a nucleic acid sequence, or a fragment of a nucleotide sequence, identified by any one of SEQ ID NO: 9-12 (Table 5; see also nucleic acid sequences of Table 7). In some embodiments, at least one PIV3 RNA (e.g., mRNA) polynucleotide comprises a nucleic acid sequence, or a fragment of a nucleotide sequence, identified by any one of SEQ ID NO: 61-64 (Table 5).

In some embodiments, at least one antigenic polypeptide is obtained from PIV3 strain HPIV3/*Homo sapiens*/PER/FLA4815/2008.

In some embodiments, at least one RSV antigenic polypeptide comprises at least one antigenic polypeptide that comprises glycoprotein G, glycoprotein F, or an immunogenic fragment thereof. In some embodiments, at least one RSV antigenic polypeptide comprises at least one antigenic polypeptide that comprises glycoprotein F and at least one or at least two antigenic polypeptide selected from G, M, N, P, L, SH, M2, NS1 and NS2.

MeV

In some embodiments, a RNA (e.g., mRNA) vaccine comprises at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one MeV antigenic polypeptide. In some embodiments, at least one antigenic polypeptide is a hemagglutinin (HA) protein or an immunogenic fragment thereof. The HA protein may be from MeV strain D3 or B8, for example. In some embodiments, at least one antigenic polypeptide is a Fusion (F) protein or an immunogenic fragment thereof. The F protein may be from MeV strain D3 or B8, for example. In some embodiments, a MeV RNA (e.g., mRNA) vaccines comprises a least one RNA polynucleotide encoding a HA protein and a F protein. The HA and F proteins may be from MeV strain D3 or B8, for example.

In some embodiments, at least one MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 (Table 14). In some embodiments, the amino acid sequence of the MeV antigenic polypeptide is, or is a fragment of, or is a homolog or variant having at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) identity to, the amino acid sequence identified by any one of SEQ ID NO: 47-50 (Table 14).

In some embodiments, at least one MeV antigenic polypeptide is encoded by a nucleic acid sequence of SEQ ID NO: 35-46 (Table 13).

In some embodiments, at least one MeV RNA (e.g., mRNA) polynucleotide is encoded by a nucleic acid sequence, or a fragment of a nucleotide sequence, identified by any one of SEQ ID NO: 35-46 (Table 13). In some embodiments, at least one MeV RNA (e.g., mRNA) polynucleotide comprises a nucleic acid sequence, or a fragment of a nucleotide sequence, identified by any one of SEQ ID NO: 69-80 (Table 13).

In some embodiments, at least one antigenic polypeptide is obtained from MeV strain B3/B3.1, C2, D4, D6, D7, D8, G3, H1, Moraten, Rubeovax, MVi/New Jersey.USA/45.05, MVi/Texas.USA/4.07, AIK-C, MVi/New York.USA/26.09/3, MVi/California.USA/16.03, MVi/Virginia.USA/15.09, MVi/California.USA/8.04, or MVi/Pennsylvania.USA/20.09.

BetaCoV

In some embodiments, a RNA (e.g., mRNA) vaccine comprises at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one BetaCoV antigenic polypeptide. In some embodiments, the BetaCoV is MERS-CoV. In some embodiments, the BetaCoV is SARS-CoV. In some embodiments, the BetaCoV is HCoV-OC43. In some embodiments, the BetaCoV is HCoV-229E. In some embodiments, the BetaCoV is HCoV-NL63. In some embodiments, the BetaCoV is HCoV-HKU1. In some embodiments, at least one antigenic polypeptide is a *Betacoronavirus* structural protein. For example, a *Betacoronavirus* structural protein may be spike protein (S), envelope protein (E), nucleocapsid protein (N), membrane protein (M) or an immunogenic fragment thereof. In some embodiments, a *Betacoronavirus* structural protein is a spike protein (S). In some embodiments, a *Betacoronavirus* structural protein is a S1 subunit or a S2 subunit of spike protein (S) or an immunogenic fragment thereof.

BetaCoV RNA (e.g., mRNA) polynucleotides of the vaccines provided herein may encode viral protein components of Betacoronaviruses, for example, accessory proteins, replicase proteins and the like are encompassed by the present disclosure. RNA (e.g., mRNA) vaccines may include RNA polynucleotides encoding at least one accessory protein (e.g., protein 3, protein 4a, protein 4b, protein 5), at least one replicase protein (e.g., protein 1a, protein 1b), or a combination of at least one accessory protein and at least one replicase protein. The present disclosure also encompasses RNA (e.g., mRNA) vaccines comprising RNA (e.g., mRNA) polynucleotides encoding an accessory protein and/or a replicase protein in combination with at least one structural protein. Due to their surface expression properties, vaccines featuring RNA polynucleotides encoding structural proteins are believed to have preferred immunogenic activity and, hence, may be most suitable for use in the vaccines of the present disclosure.

Some embodiments of the present disclosure provide *Betacoronavirus* (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH, HCoV-HKU1 or a combination thereof) vaccines that include at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one *Betacoronavirus* (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH, HCoV-HKU1) antigenic polypeptide. Also provided herein are pan-*Betacoronavirus* vaccines. Thus, a *Betacoronavirus* vaccine comprising a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding any one, two, three or four of MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, and HCoV-HKU1, for example, may be effective against any one of, any combination of, or all of, MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1. Other Betacoronaviruses are encompassed by the present disclosure.

In some embodiments, at least one antigenic polypeptide is a MERS-CoV structural protein. For example, a MERS-CoV structural protein may be spike protein (S), envelope protein (E), nucleocapsid protein (N), membrane protein (M) or an immunogenic fragment thereof. In some embodiments, the MERS-CoV structural protein is a spike protein (S) (see, e.g., Coleman C M et al. *Vaccine* 2014; 32:3169-74, incorporated herein by reference). In some embodiments, the MERS-CoV structural protein is a S1 subunit or a S2 subunit of spike protein (S) or an immunogenic fragment thereof (Li J et al. *Viral Immunol* 2013; 26(2):126-32; He Y et al. *Biochem Biophys Res Commun* 2004; 324(2):773-81, each of which is incorporated herein by reference).

In some embodiments, at least one MERS-CoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-28 or 33 (Table 11). In some embodiments, the amino acid sequence of the MERS-CoV antigenic polypeptide is, or is a fragment of, or is a homolog or variant having at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) identity to, the amino acid sequence identified by any one of SEQ ID NO: 24-28 or 33 (Table 11).

In some embodiments, at least one MERS-CoV antigenic polypeptide is encoded by a nucleic acid sequence identified by any one of SEQ ID NO: 20-23 (Table 10).

In some embodiments, at least one MERS-CoV RNA (e.g., mRNA) polynucleotide is encoded by a nucleic acid sequence, or a fragment of a nucleotide sequence, identified by any one of SEQ ID NO: 20-23 (Table 10). In some embodiments, at least one MERS-CoV RNA (e.g., mRNA) polynucleotide comprises a nucleic acid sequence, or a fragment of a nucleotide sequence, identified by any one of SEQ ID NO: 65-68 (Table 10).

In some embodiments, at least one antigenic polypeptide is obtained from MERS-CoV strain Riyadh_14_2013, 2cEMC/2012, or Hasa_1_2013.

In some embodiments, at least one antigenic polypeptide is a SARS-CoV structural protein. For example, a SARS-CoV structural protein may be spike protein (S), envelope protein (E), nucleocapsid protein (N), membrane protein (M) or an immunogenic fragment thereof. In some embodiments, the SARS-CoV structural protein is a spike protein (S). In some embodiments, the SARS-CoV structural protein is a S1 subunit or a S2 subunit of spike protein (S) or an immunogenic fragment thereof.

In some embodiments, at least one SARS-CoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 29, 32 or 34 (Table 11). In some embodiments, the amino acid sequence of the SARS-CoV antigenic polypeptide is, or is a fragment of, or is a homolog or variant having at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) identity to, the amino acid sequence identified by any one of SEQ ID NO: 29, 32 or 34 (Table 11).

In some embodiments, at least one antigenic polypeptide is a HCoV-OC43 structural protein. For example, a HCoV-OC43 structural protein may be spike protein (S), envelope protein (E), nucleocapsid protein (N), membrane protein (M) or an immunogenic fragment thereof. In some embodiments, the HCoV-OC43 structural protein is a spike protein (S). In some embodiments, the HCoV-OC43 structural protein is a S1 subunit or a S2 subunit of spike protein (S) or an immunogenic fragment thereof.

In some embodiments, at least one HCoV-OC43 antigenic polypeptide comprises an amino acid sequence identified by

any one of SEQ ID NO: 30 (Table 11). In some embodiments, the amino acid sequence of the HCoV-OC43 antigenic polypeptide is, or is a fragment of, or is a homolog or variant having at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) identity to, the amino acid sequence identified by any one of SEQ ID NO: 30 (Table 11).

In some embodiments, an antigenic polypeptide is a HCoV-HKU1 structural protein. For example, a HCoV-HKU1 structural protein may be spike protein (S), envelope protein (E), nucleocapsid protein (N), membrane protein (M) or an immunogenic fragment thereof. In some embodiments, the HCoV-HKU1 structural protein is a spike protein (S). In some embodiments, the HCoV-HKU1 structural protein is a S1 subunit or a S2 subunit of spike protein (S) or an immunogenic fragment thereof.

In some embodiments, at least one HCoV-HKU1 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 31 (Table 11). In some embodiments, the amino acid sequence of the HCoV-HKU1 antigenic polypeptide is, or is a fragment of, or is a homolog or variant having at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) identity to, the amino acid sequence identified by any one of SEQ ID NO: 31 (Table 11).

In some embodiments, an open reading frame of a RNA (e.g., mRNA) vaccine is codon-optimized. In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, or 47-50 (Tables 3, 6, 11 and 14; see also amino acid sequences of Tables 4, 7, 12 and 15) and is codon optimized mRNA.

In some embodiments, a RNA (e.g., mRNA) vaccine further comprising an adjuvant.

Tables 4, 7, 12 and 15 provide National Center for Biotechnology Information (NCBI) accession numbers of interest. It should be understood that the phrase "an amino acid sequence of Tables 4, 7, 12 and 15" refers to an amino acid sequence identified by one or more NCBI accession numbers listed in Tables 4, 7, 12 and 15. Each of the amino acid sequences, and variants having greater than 95% identity or greater than 98% identity to each of the amino acid sequences encompassed by the accession numbers of Tables 4, 7, 12 and 15 are included within the constructs (polynucleotides/polypeptides) of the present disclosure.

In some embodiments, at least one mRNA polynucleotide is encoded by a nucleic acid having a sequence identified by any one of SEQ ID NO: 1-4, 9-12, 20-23, or 35-46 (Tables 2, 5, 10 and 13; see also nucleic acid sequences of Table 7) and having less than 80% identity to wild-type mRNA sequence. In some embodiments, at least one mRNA polynucleotide is encoded by a nucleic acid having a sequence identified by any one of SEQ ID NO: 1-4, 9-12, 20-23, or 35-46 (Tables 2, 5, 10 and 13; see also nucleic acid sequences of Table 7) and having less than 75%, 85% or 95% identity to a wild-type mRNA sequence. In some embodiments, at least one mRNA polynucleotide is encoded by a nucleic acid having a sequence identified by any one of SEQ ID NO: 1-4, 9-12, 20-23, or 35-46 (Tables 2, 5, 10 and 13; see also nucleic acid sequences of Table 7) and having less than 50-80%, 60-80%, 40-80%, 30-80%, 70-80%, 75-80% or 78-80% identity to wild-type mRNA sequence. In some embodiments, at least one mRNA polynucleotide is encoded by a nucleic acid having a sequence identified by any one of SEQ ID NO: 1-4, 9-12, 20-23, or 35-46 (Tables 2, 5, 10 and 13; see also nucleic acid sequences of Table 7) and having less than 40-85%, 50-85%, 60-85%, 30-85%, 70-85%, 75-85% or 80-85% identity to wild-type mRNA sequence. In some embodiments, at least one mRNA polynucleotide is encoded by a nucleic acid having a sequence identified by any one of SEQ ID NO: 1-4, 9-12, 20-23, or 35-46 (Tables 2, 5, 10 and 13; see also nucleic acid sequences of Table 7) and having less than 40-90%, 50-90%, 60-90%, 30-90%, 70-90%, 75-90%, 80-90%, or 85-90% identity to wild-type mRNA sequence.

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, or 47-50 (Tables 3, 6, 11 and 14; see also amino acid sequences of Tables 4, 7, 12 and 15) and having at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) identity to wild-type mRNA sequence, but does not include wild-type mRNA sequence.

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, or 47-50 (Tables 3, 6, 11 and 14; see also amino acid sequences of Tables 4, 7, 12 and 15) and has less than 95%, 90%, 85%, 80% or 75% identity to wild-type mRNA sequence. In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, or 47-50 (Tables 3, 6, 11 and 14; see also amino acid sequences of Tables 4, 7, 12 and 15) and has 30-80%, 40-80%, 50-80%, 60-80%, 70-80%, 75-80% or 78-80%, 30-85%, 40-85%, 50-805%, 60-85%, 70-85%, 75-85% or 78-85%, 30-90%, 40-90%, 50-90%, 60-90%, 70-90%, 75-90%, 80-90% or 85-90% identity to wild-type mRNA sequence.

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, or 47-50 (Tables 3, 6, 11 and 14; see also amino acid sequences of Tables 4, 7, 12 and 15). In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having 95%-99% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, or 47-50 (Tables 3, 6, 11 and 14; see also amino acid sequences of Tables 4, 7, 12 and 15).

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, or 47-50 (Tables 3, 6, 11 and 14; see also amino acid sequences of Tables 4, 7, 12 and 15) and having membrane fusion activity. In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having 95%-99% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, or 47-50 (Tables 3, 6, 11 and 14; see also amino acid sequences of Tables 4, 7, 12 and 15) and having membrane fusion activity.

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide (e.g., at least one hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one RSV antigenic polypeptide, at least one MeV antigenic polypeptide, or at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides) that attaches to cell receptors.

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide (e.g., at least one

hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one RSV antigenic polypeptide, at least one MeV antigenic polypeptide, or at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides) that causes fusion of viral and cellular membranes.

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide (e.g., at least one hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one RSV antigenic polypeptide, at least one MeV antigenic polypeptide, or at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides) that is responsible for binding of the virus to a cell being infected.

Some embodiments of the present disclosure provide a vaccine that includes at least one ribonucleic acid (RNA) (e.g., mRNA) polynucleotide having an open reading frame encoding at least one antigenic polypeptide (e.g., at least one hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one RSV antigenic polypeptide, at least one MeV antigenic polypeptide, or at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides), at least one 5' terminal cap and at least one chemical modification, formulated within a lipid nanoparticle.

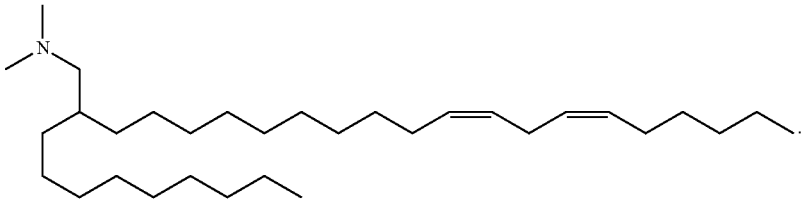
In some embodiments, a 5' terminal cap is 7mG(5')ppp(5')NlmpNp.

In some embodiments, at least one chemical modification is selected from pseudouridine, N1-methylpseudouridine, N1-ethylpseudouridine, 2-thiouridine, 4'-thiouridine, 5-methylcytosine, 5-methyluridine, 2-thio-1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-pseudouridine, 2-thio-5-aza-uridine, 2-thio-dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-pseudouridine, 4-methoxy-2-thio-pseudouridine, 4-methoxy-pseudouridine, 4-thio-1-methyl-pseudouridine, 4-thio-pseudouridine, 5-aza-uridine, dihydropseudouridine, 5-methoxyuridine and 2'-O-methyl uridine. In some embodiments, the chemical modification is in the 5-position of the uracil. In some embodiments, the chemical modification is a N1-methylpseudouridine. In some embodiments, the chemical modification is a N1-ethylpseudouridine.

In some embodiments, a lipid nanoparticle comprises a cationic lipid, a PEG-modified lipid, a sterol and a non-cationic lipid. In some embodiments, a cationic lipid is an ionizable cationic lipid and the non-cationic lipid is a neutral lipid, and the sterol is a cholesterol. In some embodiments, a cationic lipid is selected from the group consisting of 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), (12Z,15Z)—N,N-dimethyl-2-nonylhenicosa-12,15-dien-1-amine (L608), and N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]heptadecan-8-amine (L530).

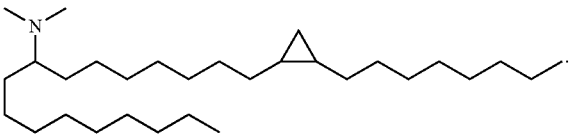
In some embodiments, the lipid is

(L608)



In some embodiments, the lipid is

(L530)



In some embodiments, a lipid nanoparticle comprises compounds of Formula (I) and/or Formula (II), discussed below.

In some embodiments, a respiratory virus RNA (e.g., mRNA) vaccine is formulated in a lipid nanoparticle that comprises a compound selected from Compounds 3, 18, 20, 25, 26, 29, 30, 60, 108-112 and 122, described below.

Some embodiments of the present disclosure provide a vaccine that includes at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one antigenic polypeptide (e.g., at least one hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one RSV antigenic polypeptide, at least one MeV antigenic polypeptide, or at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides), wherein at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) of the uracil in the open reading frame have a chemical modification, optionally wherein the vaccine is formulated in a lipid nanoparticle (e.g., a lipid nanoparticle comprises a cationic lipid, a PEG-modified lipid, a sterol and a non-cationic lipid).

In some embodiments, 100% of the uracil in the open reading frame have a chemical modification. In some embodiments, a chemical modification is in the 5-position of the uracil. In some embodiments, a chemical modification is a N1-methyl pseudouridine. In some embodiments, 100% of the uracil in the open reading frame have a N1-methyl pseudouridine in the 5-position of the uracil.

In some embodiments, an open reading frame of a RNA (e.g., mRNA) polynucleotide encodes at least two antigenic

polypeptides (e.g., at least two hMPV antigenic polypeptides, at least two PIV3 antigenic polypeptides, at least two RSV antigenic polypeptides, at least two MeV antigenic polypeptides, or at least two BetaCoV antigenic polypeptides, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides). In some embodiments, the open reading frame encodes at least five or at least ten antigenic polypeptides. In some embodiments, the open reading frame encodes at least 100 antigenic polypeptides. In some embodiments, the open reading frame encodes 2-100 antigenic polypeptides.

In some embodiments, a vaccine comprises at least two RNA (e.g., mRNA) polynucleotides, each having an open reading frame encoding at least one antigenic polypeptide (e.g., at least one hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one RSV antigenic polypeptide, at least one MeV antigenic polypeptide, or at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides). In some embodiments, the vaccine comprises at least five or at least ten RNA (e.g., mRNA) polynucleotides, each having an open reading frame encoding at least one antigenic polypeptide or an immunogenic fragment thereof. In some embodiments, the vaccine comprises at least 100 RNA (e.g., mRNA) polynucleotides, each having an open reading frame encoding at least one antigenic polypeptide. In some embodiments, the vaccine comprises 2-100 RNA (e.g., mRNA) polynucleotides, each having an open reading frame encoding at least one antigenic polypeptide.

In some embodiments, at least one antigenic polypeptide (e.g., at least one hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one RSV antigenic polypeptide, at least one MeV antigenic polypeptide, or at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides) is fused to a signal peptide. In some embodiments, the signal peptide is selected from: a HuIgGk signal peptide (METPAQLLFLLLLWLPDTTG; SEQ ID NO: 15); IgE heavy chain epsilon-1 signal peptide (MDWTWILFLVAAATRVHS; SEQ ID NO: 16); Japanese encephalitis PRM signal sequence (MLGSNSGQRVVFTILLLLVAPAYS; SEQ ID NO: 17), VSVg protein signal sequence (MKCLLYLAFLFIGVNCA; SEQ ID NO: 18) and Japanese encephalitis JEV signal sequence (MWLVSLAIVTACAGA; SEQ ID NO: 19).

In some embodiments, the signal peptide is fused to the N-terminus of at least one antigenic polypeptide. In some embodiments, a signal peptide is fused to the C-terminus of at least one antigenic polypeptide.

In some embodiments, at least one antigenic polypeptide (e.g., at least one hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one RSV antigenic polypeptide, at least one MeV antigenic polypeptide, or at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides) comprises a mutated N-linked glycosylation site.

Also provided herein is a RNA (e.g., mRNA) vaccine of any one of the foregoing paragraphs (e.g., a hMPV vaccine, a PIV3 vaccine, a RSV vaccine, a MeV vaccine, or a BetaCoV vaccine, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing vaccines), formulated in a nanoparticle (e.g., a lipid nanoparticle).

In some embodiments, the nanoparticle has a mean diameter of 50-200 nm. In some embodiments, the nanoparticle is a lipid nanoparticle. In some embodiments, the lipid nanoparticle comprises a cationic lipid, a PEG-modified lipid, a sterol and a non-cationic lipid. In some embodiments, the lipid nanoparticle comprises a molar ratio of about 20-60% cationic lipid, 0.5-15% PEG-modified lipid, 25-55% sterol, and 25% non-cationic lipid. In some embodiments, the cationic lipid is an ionizable cationic lipid and the non-cationic lipid is a neutral lipid, and the sterol is a cholesterol. In some embodiments, the cationic lipid is selected from 2,2-dilinoleyl-4-dimethylaminoethyl[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319).

In some embodiments, a lipid nanoparticle comprises compounds of Formula (I) and/or Formula (II), as discussed below.

In some embodiments, a lipid nanoparticle comprises Compounds 3, 18, 20, 25, 26, 29, 30, 60, 108-112, or 122, as discussed below.

In some embodiments, the nanoparticle has a polydispersity value of less than 0.4 (e.g., less than 0.3, 0.2 or 0.1).

In some embodiments, the nanoparticle has a net neutral charge at a neutral pH value.

In some embodiments, the respiratory virus vaccine is multivalent.

Some embodiments of the present disclosure provide methods of inducing an antigen specific immune response in a subject, comprising administering to the subject any of the RNA (e.g., mRNA) vaccine as provided herein in an amount effective to produce an antigen-specific immune response. In some embodiments, the RNA (e.g., mRNA) vaccine is a hMPV vaccine, a PIV3 vaccine, a RSV vaccine, a MeV vaccine, or a BetaCoV vaccine, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1 vaccines. In some embodiments, the RNA (e.g., mRNA) vaccine is a combination vaccine comprising a combination of any two or more of the foregoing vaccines.

In some embodiments, an antigen-specific immune response comprises a T cell response or a B cell response.

In some embodiments, a method of producing an antigen-specific immune response comprises administering to a subject a single dose (no booster dose) of a RNA (e.g., mRNA) vaccine of the present disclosure. In some embodiments, the RNA (e.g., mRNA) vaccine is a hMPV vaccine, a PIV3 vaccine, a RSV vaccine, a MeV vaccine, or a BetaCoV vaccine, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1 vaccines. In some embodiments, the RNA (e.g., mRNA) vaccine is a combination vaccine comprising a combination of any two or more of the foregoing vaccines.

In some embodiments, a method further comprises administering to the subject a second (booster) dose of a RNA (e.g., mRNA) vaccine. Additional doses of a RNA (e.g., mRNA) vaccine may be administered.

In some embodiments, the subjects exhibit a seroconversion rate of at least 80% (e.g., at least 85%, at least 90%, or at least 95%) following the first dose or the second (booster) dose of the vaccine. Seroconversion is the time period during which a specific antibody develops and becomes detectable in the blood. After seroconversion has occurred, a virus can be detected in blood tests for the antibody. During an infection or immunization, antigens enter the blood, and the immune system begins to produce antibodies in response. Before seroconversion, the antigen itself may or may not be detectable, but antibodies are considered absent. During seroconversion, antibodies are present but not yet detectable. Any time after seroconversion, the antibodies can be detected in the blood, indicating a prior or current infection.

In some embodiments, a RNA (e.g., mRNA) vaccine is administered to a subject by intradermal or intramuscular injection.

Some embodiments, of the present disclosure provide methods of inducing an antigen specific immune response in a subject, including administering to a subject a RNA (e.g., mRNA) vaccine in an effective amount to produce an antigen specific immune response in a subject. Antigen-specific immune responses in a subject may be determined, in some embodiments, by assaying for antibody titer (for titer of an antibody that binds to a hMPV, PIV3, RSV, MeV and/or BetaCoV antigenic polypeptide) following administration to the subject of any of the RNA (e.g., mRNA) vaccines of the present disclosure. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased by at least 1 log relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased by 1-3 log relative to a control.

In some embodiments, the anti-antigenic polypeptide antibody titer produced in a subject is increased at least 2 times relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased at least 5 times relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased at least 10 times relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased 2-10 times relative to a control.

In some embodiments, the control is an anti-antigenic polypeptide antibody titer produced in a subject who has not been administered a RNA (e.g., mRNA) vaccine of the present disclosure. In some embodiments, the control is an anti-antigenic polypeptide antibody titer produced in a subject who has been administered a live attenuated or inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine (see, e.g., Ren J. et al. *J of Gen. Virol.* 2015; 96: 1515-1520), or wherein the control is an anti-antigenic polypeptide antibody titer produced in a subject who has been administered a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine. In some embodiments, the control is an anti-antigenic polypeptide antibody titer produced in a subject who has been administered a hMPV, PIV3, RSV, MeV and/or BetaCoV virus-like particle (VLP) vaccine (see, e.g., Cox R G et al., *J Virol.* 2014 June; 88(11): 6368-6379).

A RNA (e.g., mRNA) vaccine of the present disclosure is administered to a subject in an effective amount (an amount effective to induce an immune response). In some embodiments, the effective amount is a dose equivalent to an at least 2-fold, at least 4-fold, at least 10-fold, at least 100-fold, at least 1000-fold reduction in the standard of care dose of a recombinant hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine, wherein the anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine, a purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine, a live attenuated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine, an inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine, or a hMPV, PIV3, RSV, MeV and/or BetaCoV VLP vaccine. In some embodiments, the effective amount is a dose equivalent to 2-1000-fold reduction in the standard of care dose of a recombinant hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine, wherein the anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine, a purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine, a live attenuated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine, an inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine, or a hMPV, PIV3, RSV, MeV and/or BetaCoV VLP vaccine.

In some embodiments, the control is an anti-antigenic polypeptide antibody titer produced in a subject who has been administered a virus-like particle (VLP) vaccine comprising structural proteins of hMPV, PIV3, RSV, MeV and/or BetaCoV.

In some embodiments, the RNA (e.g., mRNA) vaccine is formulated in an effective amount to produce an antigen specific immune response in a subject.

In some embodiments, the effective amount is a total dose of 25 μg to 1000 μg, or 50 μg to 1000 μg. In some embodiments, the effective amount is a total dose of 100 μg. In some embodiments, the effective amount is a dose of 25 μg administered to the subject a total of two times. In some embodiments, the effective amount is a dose of 100 μg administered to the subject a total of two times. In some embodiments, the effective amount is a dose of 400 μg administered to the subject a total of two times. In some embodiments, the effective amount is a dose of 500 μg administered to the subject a total of two times.

In some embodiments, the efficacy (or effectiveness) of a RNA (e.g., mRNA) vaccine is greater than 60%. In some embodiments, the RNA (e.g., mRNA) polynucleotide of the vaccine at least one hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one RSV antigenic polypeptide, at least one MeV antigenic polypeptide, at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides.

Vaccine efficacy may be assessed using standard analyses (see, e.g., Weinberg et al., *J Infect Dis.* 2010 Jun. 1; 201(11):1607-10). For example, vaccine efficacy may be measured by double-blind, randomized, clinical controlled trials. Vaccine efficacy may be expressed as a proportionate reduction in disease attack rate (AR) between the unvaccinated (ARU) and vaccinated (ARV) study cohorts and can be calculated from the relative risk (RR) of disease among the vaccinated group with use of the following formulas:

$$\text{Efficacy}=(\text{ARU}-\text{ARV})/\text{ARU}\times 100; \text{ and}$$

$$\text{Efficacy}=(1-\text{RR})\times 100.$$

Likewise, vaccine effectiveness may be assessed using standard analyses (see, e.g., Weinberg et al., *J Infect Dis.* 2010 Jun. 1; 201(11):1607-10). Vaccine effectiveness is an assessment of how a vaccine (which may have already proven to have high vaccine efficacy) reduces disease in a population. This measure can assess the net balance of benefits and adverse effects of a vaccination program, not just the vaccine itself, under natural field conditions rather than in a controlled clinical trial. Vaccine effectiveness is proportional to vaccine efficacy (potency) but is also affected by how well target groups in the population are immunized, as well as by other non-vaccine-related factors that influence the 'real-world' outcomes of hospitalizations, ambulatory visits, or costs. For example, a retrospective case control analysis may be used, in which the rates of vaccination among a set of infected cases and appropriate controls are compared. Vaccine effectiveness may be expressed as a rate difference, with use of the odds ratio (OR) for developing infection despite vaccination:

$$\text{Effectiveness}=(1-\text{OR})\times 100.$$

In some embodiments, the efficacy (or effectiveness) of a RNA (e.g., mRNA) vaccine is at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, or at least 90%.

In some embodiments, the vaccine immunizes the subject against hMPV, PIV3, RSV, MeV, BetaCoV (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1), or any combination of two or more of the foregoing viruses for up to 2 years. In some embodiments, the vaccine immunizes the subject against hMPV, PIV3, RSV, MeV, BetaCoV (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1), or any combination of two or more of the foregoing viruses for more than 2 years, more than 3 years, more than 4 years, or for 5-10 years.

In some embodiments, the subject is about 5 years old or younger. For example, the subject may be between the ages of about 1 year and about 5 years (e.g., about 1, 2, 3, 5 or 5 years), or between the ages of about 6 months and about 1 year (e.g., about 6, 7, 8, 9, 10, 11 or 12 months). In some embodiments, the subject is about 12 months or younger (e.g., 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 months or 1 month). In some embodiments, the subject is about 6 months or younger.

In some embodiments, the subject was born full term (e.g., about 37-42 weeks). In some embodiments, the subject was born prematurely, for example, at about 36 weeks of gestation or earlier (e.g., about 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26 or 25 weeks). For example, the subject may have been born at about 32 weeks of gestation or earlier. In some embodiments, the subject was born prematurely between about 32 weeks and about 36 weeks of gestation. In such subjects, a RNA (e.g., mRNA) vaccine may be administered later in life, for example, at the age of about 6 months to about 5 years, or older.

In some embodiments, the subject is pregnant (e.g., in the first, second or third trimester) when administered an RNA (e.g., mRNA) vaccine. Viruses such as hMPV, PIV3 and RSV causes infections of the lower respiratory tract, mainly in infants and young children. One-third of RSV related deaths, for example, occur in the first year of life, with 99 percent of these deaths occurring in low-resource countries. It's so widespread in the United States that nearly all children become infected with the virus before their second birthdays. Thus, the present disclosure provides RNA (e.g., mRNA) vaccines for maternal immunization to improve mother-to-child transmission of protection against the virus.

In some embodiments, the subject is a young adult between the ages of about 20 years and about 50 years (e.g., about 20, 25, 30, 35, 40, 45 or 50 years old).

In some embodiments, the subject is an elderly subject about 60 years old, about 70 years old, or older (e.g., about 60, 65, 70, 75, 80, 85 or 90 years old).

In some embodiments, the subject is has a chronic pulmonary disease (e.g., chronic obstructive pulmonary disease (COPD) or asthma). Two forms of COPD include chronic bronchitis, which involves a long-term cough with mucus, and emphysema, which involves damage to the lungs over time. Thus, a subject administered a RNA (e.g., mRNA) vaccine may have chronic bronchitis or emphysema.

In some embodiments, the subject has been exposed to hMPV, PIV3, RSV, MeV, BetaCoV (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1), or any combination of two or more of the foregoing viruses; the subject is infected with hMPV, PIV3, RSV, MeV, BetaCoV (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1), or any combination of two or more of the foregoing viruses; or subject is at risk of infection by hMPV, PIV3, RSV, MeV, BetaCoV (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1), or any combination of two or more of the foregoing viruses.

In some embodiments, the subject is immunocompromised (has an impaired immune system, e.g., has an immune disorder or autoimmune disorder).

In some embodiments the nucleic acid vaccines described herein are chemically modified. In other embodiments the nucleic acid vaccines are unmodified.

Yet other aspects provide compositions for and methods of vaccinating a subject comprising administering to the subject a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding a first respiratory virus antigenic polypeptide, wherein the RNA polynucleotide does not include a stabilization element, and wherein an adjuvant is not coformulated or co-administered with the vaccine.

In other aspects the invention is a composition for or method of vaccinating a subject comprising administering to the subject a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding a first antigenic polypeptide wherein a dosage of between 10 μg/kg and 400 μg/kg of the nucleic acid vaccine is administered to the subject. In some embodiments the dosage of the RNA polynucleotide is 1-5 μg, 5-10 μg, 10-15 μg, 15-20 μg, 10-25 μg, 20-25 μg, 20-50 μg, 30-50 μg, 40-50 μg, 40-60 μg, 60-80 μg, 60-100 μg, 50-100 μg, 80-120 μg, 40-120 μg, 40-150 μg, 50-150 μg, 50-200 μg, 80-200 μg, 100-200 μg, 120-250 μg, 150-250 μg, 180-280 μg, 200-300 μg, 50-300 μg, 80-300 μg, 100-300 μg, 40-300 μg, 50-350 μg, 100-350 μg, 200-350 μg, 300-350 μg, 320-400 μg, 40-380 μg, 40-100 μg, 100-400 μg, 200-400 μg, or 300-400 μg per dose. In some embodiments, the nucleic acid vaccine is administered to the subject by intradermal or intramuscular injection. In some embodiments, the nucleic acid vaccine is administered to the subject on day zero. In some embodiments, a second dose of the nucleic acid vaccine is administered to the subject on day twenty one.

In some embodiments, a dosage of 25 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some embodiments, a dosage

of 100 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some embodiments, a dosage of 50 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some embodiments, a dosage of 75 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some embodiments, a dosage of 150 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some embodiments, a dosage of 400 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some embodiments, a dosage of 200 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some embodiments, the RNA polynucleotide accumulates at a 100 fold higher level in the local lymph node in comparison with the distal lymph node. In other embodiments the nucleic acid vaccine is chemically modified and in other embodiments the nucleic acid vaccine is not chemically modified.

Aspects of the invention provide a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding a first antigenic polypeptide, wherein the RNA polynucleotide does not include a stabilization element, and a pharmaceutically acceptable carrier or excipient, wherein an adjuvant is not included in the vaccine. In some embodiments, the stabilization element is a histone stem-loop. In some embodiments, the stabilization element is a nucleic acid sequence having increased GC content relative to wild type sequence.

Aspects of the invention provide nucleic acid vaccines comprising one or more RNA polynucleotides having an open reading frame encoding a first antigenic polypeptide, wherein the RNA polynucleotide is present in the formulation for in vivo administration to a host, which confers an antibody titer superior to the criterion for seroprotection for the first antigen for an acceptable percentage of human subjects. In some embodiments, the antibody titer produced by the mRNA vaccines of the invention is a neutralizing antibody titer. In some embodiments the neutralizing antibody titer is greater than a protein vaccine. In other embodiments the neutralizing antibody titer produced by the mRNA vaccines of the invention is greater than an adjuvanted protein vaccine. In yet other embodiments the neutralizing antibody titer produced by the mRNA vaccines of the invention is 1,000-10,000, 1,200-10,000, 1,400-10,000, 1,500-10,000, 1,000-5,000, 1,000-4,000, 1,800-10,000, 2000-10,000, 2,000-5,000, 2,000-3,000, 2,000-4,000, 3,000-5,000, 3,000-4,000, or 2,000-2,500. A neutralization titer is typically expressed as the highest serum dilution required to achieve a 50% reduction in the number of plaques.

Also provided are nucleic acid vaccines comprising one or more RNA polynucleotides having an open reading frame encoding a first antigenic polypeptide, wherein the RNA polynucleotide is present in a formulation for in vivo administration to a host for eliciting a longer lasting high antibody titer than an antibody titer elicited by an mRNA vaccine having a stabilizing element or formulated with an adjuvant and encoding the first antigenic polypeptide. In some embodiments, the RNA polynucleotide is formulated to produce a neutralizing antibodies within one week of a single administration. In some embodiments, the adjuvant is selected from a cationic peptide and an immunostimulatory nucleic acid. In some embodiments, the cationic peptide is protamine.

Aspects provide nucleic acid vaccines comprising one or more RNA polynucleotides having an open reading frame comprising at least one chemical modification or optionally no nucleotide modification, the open reading frame encoding a first antigenic polypeptide, wherein the RNA polynucleotide is present in the formulation for in vivo administration to a host such that the level of antigen expression in the host significantly exceeds a level of antigen expression produced by an mRNA vaccine having a stabilizing element or formulated with an adjuvant and encoding the first antigenic polypeptide.

Other aspects provide nucleic acid vaccines comprising one or more RNA polynucleotides having an open reading frame comprising at least one chemical modification or optionally no nucleotide modification, the open reading frame encoding a first antigenic polypeptide, wherein the vaccine has at least 10 fold less RNA polynucleotide than is required for an unmodified mRNA vaccine to produce an equivalent antibody titer. In some embodiments, the RNA polynucleotide is present in a dosage of 25-100 micrograms.

Aspects of the invention also provide a unit of use vaccine, comprising between 10 ug and 400 ug of one or more RNA polynucleotides having an open reading frame comprising at least one chemical modification or optionally no nucleotide modification, the open reading frame encoding a first antigenic polypeptide, and a pharmaceutically acceptable carrier or excipient, formulated for delivery to a human subject. In some embodiments, the vaccine further comprises a cationic lipid nanoparticle.

Aspects of the invention provide methods of creating, maintaining or restoring antigenic memory to a respiratory virus strain in an individual or population of individuals comprising administering to said individual or population an antigenic memory booster nucleic acid vaccine comprising (a) at least one RNA polynucleotide, said polynucleotide comprising at least one chemical modification or optionally no nucleotide modification and two or more codon-optimized open reading frames, said open reading frames encoding a set of reference antigenic polypeptides, and (b) optionally a pharmaceutically acceptable carrier or excipient. In some embodiments, the vaccine is administered to the individual via a route selected from the group consisting of intramuscular administration, intradermal administration and subcutaneous administration. In some embodiments, the administering step comprises contacting a muscle tissue of the subject with a device suitable for injection of the composition. In some embodiments, the administering step comprises contacting a muscle tissue of the subject with a device suitable for injection of the composition in combination with electroporation.

Aspects of the invention provide methods of vaccinating a subject comprising administering to the subject a single dosage of between 25 ug/kg and 400 ug/kg of a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding a first antigenic polypeptide in an effective amount to vaccinate the subject.

Other aspects provide nucleic acid vaccines comprising one or more RNA polynucleotides having an open reading frame comprising at least one chemical modification, the open reading frame encoding a first antigenic polypeptide, wherein the vaccine has at least 10 fold less RNA polynucleotide than is required for an unmodified mRNA vaccine to produce an equivalent antibody titer. In some embodiments, the RNA polynucleotide is present in a dosage of 25-100 micrograms.

Other aspects provide nucleic acid vaccines comprising an LNP formulated RNA polynucleotide having an open reading frame comprising no nucleotide modifications (unmodified), the open reading frame encoding a first antigenic

polypeptide, wherein the vaccine has at least 10 fold less RNA polynucleotide than is required for an unmodified mRNA vaccine not formulated in a LNP to produce an equivalent antibody titer. In some embodiments, the RNA polynucleotide is present in a dosage of 25-100 micrograms.

The data presented in the Examples demonstrate significant enhanced immune responses using the formulations of the invention. Both chemically modified and unmodified RNA vaccines are useful according to the invention. Surprisingly, in contrast to prior art reports that it was preferable to use chemically unmodified mRNA formulated in a carrier for the production of vaccines, it is described herein that chemically modified mRNA-LNP vaccines required a much lower effective mRNA dose than unmodified mRNA, i.e., tenfold less than unmodified mRNA when formulated in carriers other than LNP. Both the chemically modified and unmodified RNA vaccines of the invention produce better immune responses than mRNA vaccines formulated in a different lipid carrier.

In other aspects the invention encompasses a method of treating an elderly subject age 60 years or older comprising administering to the subject a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding a respiratory virus antigenic polypeptide in an effective amount to vaccinate the subject.

In other aspects the invention encompasses a method of treating a young subject age 17 years or younger comprising administering to the subject a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding a respiratory virus antigenic polypeptide in an effective amount to vaccinate the subject.

In other aspects the invention encompasses a method of treating an adult subject comprising administering to the subject a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding a respiratory virus antigenic polypeptide in an effective amount to vaccinate the subject.

In some aspects the invention is a method of vaccinating a subject with a combination vaccine including at least two nucleic acid sequences encoding respiratory antigens wherein the dosage for the vaccine is a combined therapeutic dosage wherein the dosage of each individual nucleic acid encoding an antigen is a sub therapeutic dosage. In some embodiments, the combined dosage is 25 micrograms of the RNA polynucleotide in the nucleic acid vaccine administered to the subject. In some embodiments, the combined dosage is 100 micrograms of the RNA polynucleotide in the nucleic acid vaccine administered to the subject. In some embodiments the combined dosage is 50 micrograms of the RNA polynucleotide in the nucleic acid vaccine administered to the subject. In some embodiments, the combined dosage is 75 micrograms of the RNA polynucleotide in the nucleic acid vaccine administered to the subject. In some embodiments, the combined dosage is 150 micrograms of the RNA polynucleotide in the nucleic acid vaccine administered to the subject. In some embodiments, the combined dosage is 400 micrograms of the RNA polynucleotide in the nucleic acid vaccine administered to the subject. In some embodiments, the sub therapeutic dosage of each individual nucleic acid encoding an antigen is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 micrograms. In other embodiments the nucleic acid vaccine is chemically modified and in other embodiments the nucleic acid vaccine is not chemically modified.

The RNA polynucleotide is one of SEQ ID NO: 1-4, 9-12, 20-23, 35-46, 57-61, and 64-80 and includes at least one chemical modification. In other embodiments the RNA polynucleotide is one of SEQ ID NO: 1-4, 9-12, 20-23, 35-46, 57-61, and 64-80 and does not include any nucleotide modifications, or is unmodified. In yet other embodiments the at least one RNA polynucleotide encodes an antigenic protein of any of SEQ ID NO: 5-8, 12-13, 24-34, and 47-50 and includes at least one chemical modification. In other embodiments the RNA polynucleotide encodes an antigenic protein of any of SEQ ID NO: 5-8, 12-13, 24-34, and 47-50 and does not include any nucleotide modifications, or is unmodified.

In preferred aspects, vaccines of the invention (e.g., LNP-encapsulated mRNA vaccines) produce prophylactically- and/or therapeutically-efficacious levels, concentrations and/or titers of antigen-specific antibodies in the blood or serum of a vaccinated subject. As defined herein, the term antibody titer refers to the amount of antigen-specific antibody produces in s subject, e.g., a human subject. In exemplary embodiments, antibody titer is expressed as the inverse of the greatest dilution (in a serial dilution) that still gives a positive result. In exemplary embodiments, antibody titer is determined or measured by enzyme-linked immunosorbent assay (ELISA). In exemplary embodiments, antibody titer is determined or measured by neutralization assay, e.g., by microneutralization assay. In certain aspects, antibody titer measurement is expressed as a ratio, such as 1:40, 1:100, etc.

In exemplary embodiments of the invention, an efficacious vaccine produces an antibody titer of greater than 1:40, greater that 1:100, greater than 1:400, greater than 1:1000, greater than 1:2000, greater than 1:3000, greater than 1:4000, greater than 1:500, greater than 1:6000, greater than 1:7500, greater than 1:10000. In exemplary embodiments, the antibody titer is produced or reached by 10 days following vaccination, by 20 days following vaccination, by 30 days following vaccination, by 40 days following vaccination, or by 50 or more days following vaccination. In exemplary embodiments, the titer is produced or reached following a single dose of vaccine administered to the subject. In other embodiments, the titer is produced or reached following multiple doses, e.g., following a first and a second dose (e.g., a booster dose.)

In exemplary aspects of the invention, antigen-specific antibodies are measured in units of μg/ml or are measured in units of IU/L (International Units per liter) or mIU/ml (milli International Units per ml). In exemplary embodiments of the invention, an efficacious vaccine produces >0.5 μg/ml, >0.1 μg/ml, >0.2 μg/ml, >0.35 μg/ml, >0.5 μg/ml, >1 μg/ml, >2 μg/ml, >5 μg/ml or >10 μg/ml. In exemplary embodiments of the invention, an efficacious vaccine produces >10 mIU/ml, >20 mIU/ml, >50 mIU/ml, >100 mIU/ml, >200 mIU/ml, >500 mIU/ml or >1000 mIU/ml. In exemplary embodiments, the antibody level or concentration is produced or reached by 10 days following vaccination, by 20 days following vaccination, by 30 days following vaccination, by 40 days following vaccination, or by 50 or more days following vaccination. In exemplary embodiments, the level or concentration is produced or reached following a single dose of vaccine administered to the subject. In other embodiments, the level or concentration is produced or reached following multiple doses, e.g., following a first and a second dose (e.g., a booster dose.) In exemplary embodiments, antibody level or concentration is determined or measured by enzyme-linked immunosorbent assay (ELISA). In exemplary embodiments, antibody level or concentration is determined or measured by neutralization assay, e.g., by microneutralization assay.

The details of various embodiments of the disclosure are set forth in the description below. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other objects, features and advantages will be apparent from the following description of particular embodiments of the disclosure, as illustrated in the accompanying drawings in which like reference characters refer to the same parts throughout the different views. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating the principles of various embodiments of the disclosure.

FIG. **1** shows a schematic of one example of a RNA (e.g. mRNA) vaccine construct of the present disclosure. The construct depicts a human *Metapneumovirus* and human respiratory syncytial virus full length fusion protein obtained from wild-type strains (*The Journal of General Virology*. 2008; 89(Pt 12): 3113-3118, incorporated herein by reference).

FIGS. **2**A-**2**C are graphs showing the levels of anti-hMPV fusion protein-specific antibodies in the serum of mice immunized with hMPV mRNA vaccines on day 0 (FIG. **2**A), day 14 (FIG. **2**B) and day 35 (FIG. **2**C) post immunization. The mice were immunized with a single dose (2 μg or 10 μg) on day 0 and were given a boost dose (2 μg or 10 μg) on day 21, hMPV fusion protein-specific antibodies were detected at up to 1:10000 dilution of serum on day 35 for both doses.

FIGS. **3**A-**3**C are graphs showing the result of IgG isotyping in the serum of mice immunized with hMPV mRNA vaccines. The levels of hMPV fusion protein-specific IgG2a (FIG. **3**A) and IgG1 (FIG. **3**B) antibodies in the serum are measured by ELISA. FIG. **3**C shows that hMPV fusion protein mRNA vaccine induced a mixed Th1/Th2 cytokine response with a Th1 bias.

FIG. **4** is a graph showing in vitro neutralization of a hMPV B2 strain (TN/91-316) using the sera of mice immunized with a mRNA vaccine encoding hMPV fusion protein. Mouse serum obtained from mice receiving a 10 μg or a 2 μg dose contained hMPV-neutralizing antibodies.

FIGS. **5**A-**5**C are graphs showing a Th1 cytokine response induced by a hMPV fusion peptide pool (15-mers-50 (overlap)) in splenocytes isolated from mice immunized with the hMPV mRNA vaccines. Virus-free media was used as a negative control and Concanavalin A (ConA, a positive control for splenocyte stimulation) was included. The cytokines tested included IFN-γ (FIG. **5**A), IL-2 (FIG. **5**B) and IL12 (FIG. **5**C).

FIGS. **6**A-**6**E are graphs showing the Th2 cytokine response induced by a hMPV fusion peptide pool (15-mers-50) in splenocytes isolated from mice immunized with the hMPV mRNA vaccines. Virus-free media was used as a negative control and Concanavalin A was also included. The cytokines tested included IL-10 (FIG. **6**A), TNF-α (FIG. **6**B), IL4 (FIG. **6**C), IL-5 (FIG. **6**D) and IL-6 (FIG. **6**E).

FIGS. **7**A-**7**C are graphs showing the Th1 response induced by inactivated hMPV virus in splenocytes isolated from mice immunized with hMPV mRNA vaccines. Virus-free media was used as a negative control and Concanavalin A was included. The cytokines tested included IFN-γ (FIG. **7**A), IL-2 (FIG. **7**B) and IL12 (FIG. **7**C).

FIGS. **8**A-**8**E are graphs showing the Th2 response induced by inactivated hMPV virus in splenocytes isolated from mice immunized with the hMPV mRNA vaccines. Virus-free media was used as a negative control and Concanavalin A was included. The cytokines tested include IL-10 (FIG. **8**A), TNF-α (FIG. **8**B), IL4 (FIG. **8**C), IL-5 (FIG. **8**D) and IL-6 (FIG. **8**E).

FIGS. **9**A-**9**B are graphs showing the results of cotton rat challenge experiments. Two different doses of the hMPV mRNA vaccines were used (2 μg or 10 μg doses) to immunize the cotton rats before challenge. The hMPV mRNA vaccines reduced the viral titer in the lung and nose of the cotton rat, with the 10 μg dose being more effective in reducing viral titer. Use of a 10 μg dose resulted in 100% protection in the lung and a 2 log reduction in nose viral titer. Use of a 2 μg dose resulted in a 1 log reduction in lung vital titer and no reduction in nose viral titer. The vaccine was administered on Day 0, and a boost was administered on Day 21.

FIG. **10** is a graph showing the lung histopathology of cotton rats that received hMPV mRNA vaccines. Pathology associated with vaccine-enhanced disease was not observed in immunized groups.

FIG. **11** is a graph showing hMPV neutralization antibody titers in cotton rats that received hMPV mRNA vaccines (2 μg or 10 μg doses) on days 35 and 42 post immunization.

FIG. **12** is a graph showing the lung and nose viral load in cotton rats challenged with a hMPV/A2 strain after immunization with the indicated mRNA vaccines (hMPV mRNA vaccine or hMPV/PIV mRNA combination vaccine). Vaccinated cotton rats showed reduced lung and nose viral loads after challenge, compared to control.

FIG. **13** is a graph showing the lung and nose viral load in cotton rats challenged with PIV3 strain after immunization with indicated mRNA vaccines (PIV mRNA vaccine or hMPV/PIV combination vaccine). Vaccinated cotton rats showed reduced lung and nose viral loads after challenge, compared to control.

FIG. **14** is a graph showing hMPV neutralizing antibody titers in cotton rats that received different dosages of hMPV mRNA vaccines or hMPV/PIV combination mRNA vaccines on day 42 post immunization. The dosages of the vaccine are indicated in Table 9.

FIG. **15** is a graph showing PIV3 neutralizing antibody titers in cotton rats that received different dosages of PIV mRNA vaccines or hMPV/PIV combination mRNA vaccines on day 42 post immunization. The dosages of the vaccine are indicated in Table 9.

FIG. **16** is a graph showing the lung histopathology score of cotton rats immunized with hMPV mRNA vaccines, PIV mRNA vaccines or hMPV/PIV combination mRNA vaccines as indicated in Table 9. Low occurrence of alevolitis and interstitial pneumonia was observed, indicating no antibody-dependent enhancement (ADE) of hMPV associated diseases.

FIG. **17** is a graph showing the reciprocal MERS-CoV neutralizing antibody titers in mice immunized with *Betacoronavirus* mRNA vaccine encoding the MERS-CoV full-length Spike protein, on days 0, 21, 42, and 56 post immunization.

FIG. **18** is a graph showing the reciprocal MERS-CoV neutralizing antibody titers in mice immunized with *Betacoronavirus* mRNA vaccine encoding either the MERS-CoV full-length Spike protein, or the S2 subunit of the Spike protein. The full length spike protein induced a stronger immune response compared to the S2 subunit alone.

FIGS. **19**A-**19**C are graphs showing the viral load in the nose and throat, the bronchoalveolar lavage (BAL), or the lungs of New Zealand white rabbits 4 days post challenge with MERS-CoV. The New Zealand white rabbits were immunized with one 20 μg-dose (on day 0) or two 20

μg-doses (on day 0 and 21) of MERS-CoV mRNA vaccine encoding the full-length Spike protein before challenge. FIG. **19**A shows that two doses of MERS-CoV mRNA vaccine resulted in a 3 log reduction of viral load in the nose and led to complete protection in the throat of the New Zealand white rabbits. FIG. **19**B shows that two doses of MERS-CoV mRNA vaccine resulted in a 4 log reduction of viral load in the BAL of the New Zealand white rabbits. FIG. **19**C show one dose of MERS-CoV mRNA vaccine resulted in a 2 log reduction of viral load, while two doses of MERS-CoV mRNA vaccine resulted in an over 4 log reduction of viral load in the lungs of the New Zealand white rabbits.

FIGS. **20**A-**20**B are images and graphs showing viral load or replicating virus detected by PCR in the lungs of New Zealand white rabbits 4 days post challenge with MERS-CoV. The New Zealand white rabbits were immunized with a single 20 μg dose (on day 0, Group 1a) of MERS-CoV mRNA vaccine encoding the full-length Spike protein, two 20 μg doses (on day 0 and 21, Group 1b) of MERS-CoV mRNA vaccine encoding the full-length Spike protein, or placebo (Group 2) before challenge. FIG. **20**A shows that two doses of 20 μg a MERS-CoV mRNA vaccine reduced over 99% (2 log) of viruses in the lungs of New Zealand white rabbits. FIG. **20**B shows that the group of New Zealand white rabbits that received 2 doses of 20 μg MERS-CoV mRNA vaccine did not have any detectable replicating MERS-CoV virus in their lungs.

FIG. **21** is a graph showing the MERS-CoV neutralizing antibody titers in New Zealand white rabbits immunized with MERS-CoV mRNA vaccine encoding the full-length Spike protein. Immunization of the in New Zealand white rabbits were carried out as described in FIGS. **21**A-**21**C. The results show that two doses of 20 μg MERS-CoV mRNA vaccine induced a significant amount of neutralizing antibodies against MERS-CoV (EC_{50} between 500-1000). The MERS-CoV mRNA vaccine induced antibody titer is 3-5 fold better than any other vaccines tested in the same model.

DETAILED DESCRIPTION

The present disclosure provides, in some embodiments, vaccines that comprise RNA (e.g., mRNA) polynucleotides encoding a human *Metapneumovirus* (hMPV) antigenic polypeptide, a parainfluenza virus type 3 (PIV3) antigenic polypeptide, a respiratory syncytial virus (RSV) antigenic polypeptide, a measles virus (MeV) antigenic polypeptide, or a *Betacoronavirus* antigenic polypeptide (e.g., Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV, human coronavirus (HCoV)-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH (New Haven) and HCoV-HKU1) (see, e.g., Esper F. et al. *Emerging Infectious Diseases,* 12(5), 2006; and Pyrc K. et al. *Journal of Virology,* 81(7):3051-57, 2007, the contents of each of which is here incorporated by reference in their entirety). The present disclosure also provides, in some embodiments, combination vaccines that comprise at least one RNA (e.g., mRNA) polynucleotide encoding at least two antigenic polypeptides selected from hMPV antigenic polypeptides, PIV3 antigenic polypeptides, RSV antigenic polypeptides, MeV antigenic polypeptides and BetaCoV antigenic polypeptides. Also provided herein are methods of administering the RNA (e.g., mRNA) vaccines, methods of producing the RNA (e.g., mRNA) vaccines, compositions (e.g., pharmaceutical compositions) comprising the RNA (e.g., mRNA) vaccines, and nucleic acids (e.g., DNA) encoding the RNA (e.g., mRNA) vaccines. In some embodiments, a RNA (e.g., mRNA) vaccine comprises an adjuvant, such as a flagellin adjuvant, as provided herein.

The RNA (e.g., mRNA) vaccines (e.g., hMPV, PIV3, RSV, MeV, BetaCoV RNA vaccines and combinations thereof), in some embodiments, may be used to induce a balanced immune response, comprising both cellular and humoral immunity, without many of the risks associated with DNA vaccination.

The entire contents of International Application No. PCT/US2015/02740 is incorporated herein by reference.

Human *Metapneumovirus* (hMPV)

hMPV shares substantial homology with respiratory syncytial virus (RSV) in its surface glycoproteins. hMPV fusion protein (F) is related to other paramyxovirus fusion proteins and appears to have homologous regions that may have similar functions. The hMPV fusion protein amino acid sequence contains features characteristic of other paramyxovirus F proteins, including a putative cleavage site and potential N-linked glycosylation sites. Paramyxovirus fusion proteins are synthesized as inactive precursors (F0) that are cleaved by host cell proteases into the biologically fusion-active F1 and F2 domains (see, e.g., Cseke G. et al. *Journal of Virology* 2007; 81(2):698-707, incorporated herein by reference). hMPV has one putative cleavage site, in contrast to the two sites established for RSV F, and only shares 34% amino acid sequence identity with RSV F. F2 is extracellular and disulfide linked to F1. Fusion proteins are type I glycoproteins existing as trimers, with two 4-3 heptad repeat domains at the N- and C-terminal regions of the protein (HR1 and HR2), which form coiled-coil alpha-helices. These coiled coils become apposed in an antiparallel fashion when the protein undergoes a conformational change into the fusogenic state. There is a hydrophobic fusion peptide N proximal to the N-terminal heptad repeat, which is thought to insert into the target cell membrane, while the association of the heptad repeats brings the transmembrane domain into close proximity, inducing membrane fusion (see, e.g., Baker, K A et al. *Mol. Cell* 1999; 3:309-319). This mechanism has been proposed for a number of different viruses, including RSV, influenza virus, and human immunodeficiency virus. Fusion proteins are major antigenic determinants for all known paramyxoviruses and for other viruses that possess similar fusion proteins such as human immunodeficiency virus, influenza virus, and Ebola virus.

In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding hMPV fusion protein (F). In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding a F1 or F2 subunit of a hMPV F protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding hMPV glycoprotein (G). In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding hMPV matrix protein (M). In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding hMPV phosphoprotein (P). In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding hMPV nucleoprotein (N). In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding hMPV SH protein (SH).

In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein, M protein, P protein, N protein and SH protein.

In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and G protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and M protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and P protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and N protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and SH protein.

In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein and M protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein and P protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein and N protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein and SH protein.

In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and M protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and P protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and N protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and SH protein.

A hMPV vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one hMPV antigenic polypeptide identified by any one of SEQ ID NO: 5-8 (Table 3; see also amino acid sequences of Table 4).

A hMPV vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide encoded by a nucleic acid (e.g., DNA) identified by any one of SEQ ID NO: 1-4 (Table 2).

The present disclosure is not limited by a particular strain of hMPV. The strain of hMPV used in a vaccine may be any strain of hMPV. Non-limiting examples of strains of hMPV for use as provide herein include the CAN98-75 (CAN75) and the CAN97-83 (CAN83) hMPV strains (Skiadopoulos M H et al. *J Virol.* 20014; 78(13)6927-37, incorporated herein by reference), a hMPV A1, A2, B1 or B2 strain (see, e.g., de Graaf M et al. *The Journal of General Virology* 2008; 89:975-83; Peret T C T et al. *The Journal of Infectious Disease* 2002; 185:1660-63, incorporated herein by reference), a hMPV isolate TN/92-4 (e.g., SEQ ID NO: 1 and 5), a hMPV isolate NL/1/99 (e.g., SEQ ID NO: 2 and 6), or a hMPV isolate PER/CFI0497/2010/B (e.g., SEQ ID NO: 3 and 7).

In some embodiments, at least one hMPV antigenic polypeptide is obtained from a hMPV A1, A2, B1 or B2 strain (see, e.g., de Graaf M et al. *The Journal of General Virology* 2008; 89:975-83; Peret T C T et al. *The Journal of Infectious Disease* 2002; 185:1660-63, incorporated herein by reference). In some embodiments, at least one antigenic polypeptide is obtained from the CAN98-75 (CAN75) hMPV strain. In some embodiments, at least one antigenic polypeptide is obtained from the CAN97-83 (CAN83) hMPV strain. In some embodiments, at least one antigenic polypeptide is obtained from hMPV isolate TN/92-4 (e.g., SEQ ID NO: 1 and 5). In some embodiments, at least one antigenic polypeptide is obtained from hMPV isolate NL/1/99 (e.g., SEQ ID NO: 2 and 6). In some embodiments, at least one antigenic polypeptide is obtained from hMPV isolate PER/CFI0497/2010/B (e.g., SEQ ID NO: 3 and 7).

In some embodiments, hMPV vaccines comprise RNA (e.g., mRNA) polynucleotides encoding a hMPV antigenic polypeptides having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with hMPV F protein and having F protein activity.

A protein is considered to have F protein activity if, for example, the protein acts to fuse the viral envelope and host cell plasma membrane, mediates viral entry into a host cell via an interaction with arginine-glycine-aspartate RGD-binding integrins, or a combination thereof (see, e.g., Cox R G et al. *J Virol.* 2012; 88(22):12148-60, incorporated herein by reference).

In some embodiments, hMPV vaccines comprise RNA (e.g., mRNA) polynucleotides encoding hMPV antigenic polypeptides having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with hMPV G protein and having G protein activity.

A protein is considered to have G protein activity if, for example, the protein acts to modulate (e.g., inhibit) hMPV-induced cellular (immune) responses (see, e.g., Bao X et al. *PLoS Pathog.* 2008; 4(5):e1000077, incorporated herein by reference).

Human parainfluenza virus type 3 (PIV3)

Parainfluenza viruses belong to the family Paramyxoviridae. These are enveloped viruses with a negative-sense single-stranded RNA genome. Parainfluenza viruses belong to the subfamily Paramyxoviridae, which is subdivided into three genera: *Respirovirus* (PIV-1, PIV-3, and Sendai virus (SeV)), *Rubulavirus* (PIV-2, PIV-4 and mumps virus) and *Morbillivirus* (measles virus, rinderpest virus and canine distemper virus (CDV)). Their genome, a ~15 500 nucleotide-long negative-sense RNA molecule, encodes two envelope glycoproteins, the hemagglutinin-neuraminidase (HN), the fusion protein (F or F0), which is cleaved into F1 and F2 subunits, a matrix protein (M), a nucleocapsid protein (N) and several nonstructural proteins including the viral replicase (L). All parainfluenza viruses, except for PIV-1, express a non-structural V protein that blocks IFN signaling in the infected cell and acts therefore as a virulence factor (see, e.g., Nishio M et al. *J Virol.* 2008; 82(13):6130-38).

PIV3 hemagglutinin-neuraminidase (HN), a structural protein, is found on the viral envelope, where it is necessary for attachment and cell entry. It recognizes and binds to sialic acid-containing receptors on the host cell's surface. As a neuroaminidase, HN removes sialic acid from virus particles, preventing self-aggregation of the virus, and promoting the efficient spread of the virus. Furthermore, HN promotes the activity of the fusion (F or F0) protein, contributing to the penetration of the host cell's surface.

PIV3 fusion protein (PIV3 F) is located on the viral envelope, where it facilitates the viral fusion and cell entry. The F protein is initially inactive, but proteolytic cleavage leads to its active forms, F1 and F2, which are linked by disulfide bonds. This occurs when the HN protein binds its receptor on the host cell's surface. During early phases of

infection, the F glycoprotein mediates penetration of the host cell by fusion of the viral envelope to the plasma membrane. In later stages of the infection, the F protein facilitates the fusion of the infected cells with neighboring uninfected cells, which leads to the formation of a syncytium and spread of the infection.

PIV3 matrix protein (M) is found within the viral envelope and assists with viral assembly. It interacts with the nucleocapsid and envelope glycoproteins, where it facilitates the budding of progeny viruses through its interactions with specific sites on the cytoplasmic tail of the viral glycoproteins and nucleocapsid. It also plays a role in transporting viral components to the budding site.

PIV3 phosphoprotein (P) and PIV3 large polymerase protein (L) are found in the nucleocapsid where they form part of the RNA polymerase complex. The L protein, a viral RNA-dependent RNA polymerase, facilitates genomic transcription, while the host cell's ribosomes translate the viral mRNA into viral proteins.

PIV3 V is a non-structural protein that blocks IFN signaling in the infected cell, therefore acting as a virulence factor.

PIV3 nucleoprotein (N) encapsidates the genome in a ratio of 1 N per 6 ribonucleotides, protecting it from nucleases. The nucleocapsid (NC) has a helical structure. The encapsidated genomic RNA is termed the NC and serves as template for transcription and replication. During replication, encapsidation by PIV3 N is coupled to RNA synthesis and all replicative products are resistant to nucleases. PIV3 N homo-multimerizes to form the nucleocapsid and binds to viral genomic RNA. PIV3 N binds the P protein and thereby positions the polymerase on the template.

In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding PIV3 fusion protein (F). In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding a F1 or F2 subunit of a PIV3 F protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding PIV3 hemagglutinin-neuraminidase (HN) (see, e.g., van Wyke Coelingh K L et al. *J Virol.* 1987; 61(5):1473-77, incorporated herein by reference). In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding PIV3 matrix protein (M). In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding PIV3 phosphoprotein (P). In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding PIV3 nucleoprotein (N).

In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, HN protein, M protein, P protein, and N protein.

In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and HN protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and M protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and P protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and N protein.

In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HN protein and M protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HN protein and P protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HN protein and N protein.

In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, HN protein and M protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, HN protein and P protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, HN protein and N protein.

A PIV3 vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one PIV3 antigenic polypeptide identified by any one of SEQ ID NO: 12-13 (Table 6; see also amino acid sequences of Table 7).

A PIV3 vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide encoded by a nucleic acid (e.g., DNA) identified by any one of SEQ ID NO: 9-12 (Table 5; see also nucleic acid sequences of Table 7).

The present disclosure is not limited by a particular strain of PIV3. The strain of PIV3 used in a vaccine may be any strain of PIV3. A non-limiting example of a strain of PIV3 for use as provide herein includes HPIV3/*Homo sapiens*/PER/FLA4815/2008.

In some embodiments, PIV3 vaccines comprise RNA (e.g., mRNA) polynucleotides encoding a PIV3 antigenic polypeptides having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with PIV3 F protein and having F protein activity.

In some embodiments, PIV3 vaccines comprise RNA (e.g., mRNA) polynucleotides encoding PIV3 antigenic polypeptides having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with PIV3 hemagglutinin-neuraminidase (HN) and having hemagglutinin-neuraminidase activity.

A protein is considered to have hemagglutinin-neuraminidase activity if, for example, it is capable of both receptor binding and receptor cleaving. Such proteins are major surface glycoproteins that have functional sites for cell attachment and for neuraminidase activity. They are able to cause red blood cells to agglutinate and to cleave the glycosidic linkages of neuraminic acids, so they have the potential to both bind a potential host cell and then release the cell if necessary, for example, to prevent self-aggregation of the virus.

In some embodiments, PIV3 vaccines comprise RNA (e.g., mRNA) polynucleotides encoding PIV3 antigenic polypeptides having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with PIV3 HN, F (e.g., F, F1 or F2), M, N, L or V and having HN, F (e.g., F, F1 or F2), M, N, L or V activity, respectively.

Respiratory Syncytial Virus (RSV)

RSV is a negative-sense, single-stranded RNA virus of the genus *Pneumovirinae*. The virus is present in at least two antigenic subgroups, known as Group A and Group B, primarily resulting from differences in the surface G glycoproteins. Two RSV surface glycoproteins—G and F—mediate attachment with and attachment to cells of the respiratory epithelium. F surface glycoproteins mediate coalescence of neighboring cells. This results in the formation of syncytial cells. RSV is the most common cause of bronchiolitis. Most infected adults develop mild cold-like

symptoms such as congestion, low-grade fever, and wheezing. Infants and small children may suffer more severe symptoms such as bronchiolitis and pneumonia. The disease may be transmitted among humans via contact with respiratory secretions.

The genome of RSV encodes at least three surface glycoproteins, including F, G, and SH, four nucleocapsid proteins, including L, P, N, and M2, and one matrix protein, M. Glycoprotein F directs viral penetration by fusion between the virion and the host membrane. Glycoprotein G is a type II transmembrane glycoprotein and is the major attachment protein. SH is a short integral membrane protein. Matrix protein M is found in the inner layer of the lipid bilayer and assists virion formation. Nucleocapsid proteins L, P, N, and M2 modulate replication and transcription of the RSV genome. It is thought that glycoprotein G tethers and stabilizes the virus particle at the surface of bronchial epithelial cells, while glycoprotein F interacts with cellular glycosaminoglycans to mediate fusion and delivery of the RSV virion contents into the host cell (Krzyzaniak M A et al. *PLoS Pathog* 2013; 9(4)).

In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding L protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding P protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding N protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding M2 protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding M protein.

In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein, L protein, P protein, N protein, M2 protein and M protein.

In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and G protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and L protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and P protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and N protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and M2 protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and M protein.

In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein and L protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein and P protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein and N protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein and M2 protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein and M protein.

In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and L protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and P protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and N protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and M2 protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and M protein.

The present disclosure is not limited by a particular strain of RSV. The strain of RSV used in a vaccine may be any strain of RSV.

In some embodiments, RSV vaccines comprise RNA (e.g., mRNA) polynucleotides encoding a RSV antigenic polypeptides having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with RSV F protein and having F protein activity.

In some embodiments, RSV vaccines comprise RNA (e.g., mRNA) polynucleotides encoding RSV antigenic polypeptides having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with RSV G protein and having G protein activity.

A protein is considered to have G protein activity if, for example, the protein acts to modulate (e.g., inhibit) hMPV-induced cellular (immune) responses (see, e.g., Bao X et al. *PLoS Pathog.* 2008; 4(5):e1000077, incorporated herein by reference).

Measles Virus (MeV)

Molecular epidemiologic investigations and virologic surveillance contribute notably to the control and prevention of measles. Nearly half of measles-related deaths worldwide occur in India, yet virologic surveillance data are incomplete for many regions of the country. Previous studies have documented the presence of measles virus genotypes D4, D7, and D8 in India, and genotypes D5, D9, D11, H1, and G3 have been detected in neighboring countries. Recently, MeV genotype B3 was detected in India (Kuttiatt V S et al. *Emerg Infect Dis.* 2014; 20(10): 1764-66).

The glycoprotein complex of paramyxoviruses mediates receptor binding and membrane fusion. In particular, the MeV fusion (F) protein executes membrane fusion, after receptor binding by the hemagglutinin (HA) protein (Muhlebach M D et al. *Journal of Virology* 2008; 82(22):11437-45). The MeV P gene codes for three proteins: P, an essential polymerase cofactor, and V and C, which have multiple functions but are not strictly required for viral propagation in cultured cells. V shares the amino-terminal domain with P but has a zinc-binding carboxyl-terminal domain, whereas C is translated from an overlapping reading frame. The MeV C protein is an infectivity factor. During replication, the P protein binds incoming monomeric nucleocapsid (N) proteins with its amino-terminal domain and positions them for assembly into the nascent ribonucleocapsid. The P protein amino-terminal domain is natively unfolded (Deveaux P et al. *Journal of Virology* 2004; 78(21):11632-40).

In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein. In some embodiments, a MeV vaccine

of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding P protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding V protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding C protein.

In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein, F protein, P protein, V protein and C protein.

In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein and F protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein and P protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein and V protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein and C protein.

some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and P protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and V protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and C protein.

In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein, F protein and P protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein, F protein and V protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein, F protein and C protein.

In some embodiments, MeV vaccines comprise RNA (e.g., mRNA) encoding a MeV antigenic polypeptide having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with MeV HA protein and having MeV HA protein activity.

In some embodiments, MeV vaccines comprise RNA (e.g., mRNA) encoding a MeV antigenic polypeptide having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with MeV F protein and having MeV F protein activity.

A protein is considered to have HA protein activity if the protein mediates receptor binding and/or membrane fusion. MeV F protein executes membrane fusion, after receptor binding by the MeV HA protein.

A MeV vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one MeV antigenic polypeptide identified by any one of SEQ ID NO: 47-50 (Table 14; see also amino acid sequences of Table 15).

A MeV vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide identified by any one of SEQ ID NO: 37, 40, 43, 46 (Table 13).

A MeV vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide encoded by a nucleic acid (e.g., DNA) identified by any one of SEQ ID NO: 35, 36, 38, 39, 41, 42, 44 and 45 (Table 13).

The present disclosure is not limited by a particular strain of MeV. The strain of MeV used in a vaccine may be any strain of MeV. Non-limiting examples of strains of MeV for use as provide herein include B3/B3.1, C2, D4, D6, D7, D8, G3, H1, Moraten, Rubeovax, MVi/New Jersey.USA/45.05, MVi/Texas.USA/4.07, AIK-C, MVi/New York.USA/26.09/3, MVi/California.USA/16.03, MVi/Virginia.USA/15.09, MVi/California.USA/8.04, and MVi/Pennsylvania.USA/20.09.

MeV proteins may be from MeV genotype D4, D5, D7, D8, D9, D11, H1, G3 or B3. In some embodiments, a MeV HA protein or a MeV F protein is from MeV genotype D8. In some embodiments, a MeV HA protein or a MeV F protein is from MeV genotype B3.

Betacoronaviruses (BetaCoV)

MERS-Co V. MERS-CoV is a positive-sense, single-stranded RNA virus of the genus *Betacoronavirus*. The genomes are phylogenetically classified into two clades, clade A and clade B. It has a strong tropism for non-ciliated bronchial epithelial cells, evades the innate immune response and antagonizes interferon (IFN) production in infected cells. Dipeptyl peptidase 4 (DDP4, also known as CD26) has been identified as a functional cellular receptor for MERS-CoV. Its enzymatic activity is not required for infection, although its amino acid sequence is highly conserved across species and is expressed in the human bronchial epithelium and kidneys. Most infected individuals develop severe acute respiratory illnesses, including fever, cough, and shortness of breath, and the virus can be fatal. The disease may be transmitted among humans, generally among those in close contact.

The genome of MERS-CoV encodes at least four unique accessory proteins, such as 3, 4a, 4b and 5, two replicase proteins (open reading frame 1a and 1b), and four major structural proteins, including spike (S), envelope (E), nucleocapsid (N), and membrane (M) proteins (Almazan F et al. *MBio* 2013; 4(5):e00650-13). The accessory proteins play nonessential roles in MERS-CoV replication, but they are likely structural proteins or interferon antagonists, modulating in vivo replication efficiency and/or pathogenesis, as in the case of SARS-CoV (Almazan F et al. *MBio* 2013; 4(5):e00650-13; Totura A L et al. *Curr Opin Virol* 2012; 2(3):264-75; Scobey T et al. *Proc Natl Acad Sci USA* 2013; 110(40):16157-62). The other proteins of MERS-CoV maintain different functions in virus replication. The E protein, for example, involves in virulence, and deleting the E-coding gene results in replication-competent and propagation-defective viruses or attenuated viruses (Almazan F et al. *MBio* 2013; 4(5):e00650-13). The S protein is particularly essential in mediating virus binding to cells expressing receptor dipeptidyl peptidase-4 (DPP4) through receptor-binding domain (RBD) in the S1 subunit, whereas the S2 subunit subsequently mediates virus entry via fusion of the virus and target cell membranes (Li F. *J Virol* 2015; 89(4): 1954-64; Raj V S et al. *Nature* 2013; 495(7440):251-4).

In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding the S1 subunit of the S protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding the S2 subunit of the S protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding E protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a

RNA (e.g., mRNA) polynucleotide encoding N protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding M protein.

In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2), E protein, N protein and M protein.

In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2) and E protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2) and N protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2) and M protein.

In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2), E protein and M protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2), E protein and N protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2), M protein and N protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding E protein, M protein and N protein.

A MERS-CoV vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one MERS-CoV antigenic polypeptide identified by any one of SEQ ID NO: 24-38 or 33 (Table 11; see also amino acid sequences of Table 12).

A MERS-CoV vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide encoded by a nucleic acid (e.g., DNA) identified by any one of SEQ ID NO: 20-23 (Table 10).

The present disclosure is not limited by a particular strain of MERS-CoV. The strain of MERS-CoV used in a vaccine may be any strain of MERS-CoV. Non-limiting examples of strains of MERS-CoV for use as provide herein include Riyadh_14_2013, and 2cEMC/2012, Hasa_1_2013.

SARS-CoV. The genome of SARS-CoV includes of a single, positive-strand RNA that is approximately 29,700 nucleotides long. The overall genome organization of SARS-CoV is similar to that of other coronaviruses. The reference genome includes 13 genes, which encode at least 14 proteins. Two large overlapping reading frames (ORFs) encompass 71% of the genome. The remainder has 12 potential ORFs, including genes for structural proteins S (spike), E (small envelope), M (membrane), and N (nucleocapsid). Other potential ORFs code for unique putative SARS-CoV-specific polypeptides that lack obvious sequence similarity to known proteins. A detailed analysis of the SARS-CoV genome has been published in *J Mol Biol* 2003; 331: 991-1004.

In some embodiments, a SARS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2), E protein, N protein and M protein.

In some embodiments, a SARS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2) and E protein. In some embodiments, a SARS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2) and N protein. In some embodiments, a SARS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2) and M protein.

In some embodiments, a SARS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2), E protein and M protein. In some embodiments, a SARS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2), E protein and N protein. In some embodiments, a SARS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2), M protein and N protein. In some embodiments, a SARS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding E protein, M protein and N protein.

A SARS-CoV vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one SARS-CoV antigenic polypeptide identified by any one of SEQ ID NO: 29, 32 or 34 (Table 11; see also amino acid sequences of Table 12).

The present disclosure is not limited by a particular strain of SARS-CoV. The strain of SARS-CoV used in a vaccine may be any strain of SARS-CoV.

HCoV-OC43. Human coronavirus OC43 is an enveloped, positive-sense, single-stranded RNA virus in the species *Betacoronavirus*-1 (genus *Betacoronavirus*, subfamily Coronavirinae, family Coronaviridae, order Nidovirales). Four HCoV-OC43 genotypes (A to D), have been identified with genotype D most likely arising from recombination. The complete genome sequencing of two genotype C and D strains and bootscan analysis shows recombination events between genotypes B and C in the generation of genotype D. Of 29 strains identified, none belong to the more ancient genotype A. Along with HCoV-229E, a species in the *Alphacoronavirus* genus, HCoV-OC43 are among the known viruses that cause the common cold. Both viruses can cause severe lower respiratory tract infections, including pneumonia in infants, the elderly, and immunocompromised individuals such as those undergoing chemotherapy and those with HIV-AIDS.

HCoV-HKU1. Human coronavirus HKU1 (HCoV-HKU1) is a positive-sense, single-stranded RNA virus with the HE gene, which distinguishes it as a group 2, or *Betacoronavirus*. It was discovered in January 2005 in two patients in Hong Kong. The genome of HCoV-HKU1 is a 29,926-nucleotide, polyadenylated RNA. The GC content is 32%, the lowest among all known coronaviruses. The genome organization is the same as that of other group II coronaviruses, with the characteristic gene order 1a, 1b, HE, S, E, M, and N. Furthermore, accessory protein genes are present between the S and E genes (ORF4) and at the position of the N gene (ORF8). The TRS is presumably located within the AAUCUAAAC sequence, which precedes each ORF except E. As in sialodacryoadenitis virus and mouse hepatitis virus (MHV), translation of the E protein possibly occurs via an internal ribosomal entry site. The 3' untranslated region contains a predicted stem-loop structure immediately downstream of the N ORF (nucleotide position 29647 to 29711). Further downstream, a pseudoknot structure is present at nucleotide position 29708 to 29760. Both RNA structures are conserved in group II coronaviruses and are critical for virus replication.

HCoV-NL63. The RNA genome of human coronavirus NL63 (HCoV-NL63) is 27,553 nucleotides, with a poly(A) tail (FIG. **1**). With a GC content of 34%, HCoV-NL63 has one of the lowest GC contents of the coronaviruses, for which GC content ranges from 32 to 42%. Untranslated regions of 286 and 287 nucleotides are present at the 5' and 3' termini, respectively. Genes predicted to encode the S, E, M, and N proteins are found in the 3' part of the HCoV-NL63 genome. The HE gene, which is present in some group II coronaviruses, is absent, and there is only a single, monocistronic accessory protein ORF (ORF3) located between the S and E genes. Subgenomic mRNAs are generated for all ORFs (S, ORF3, E, M, and N), and the core sequence of the TRS of HCoV-NL63 is defined as AACUAAA. This sequence is situated upstream of every ORF except for the E ORF, which contains the suboptimal core sequence AACUAUA. Interestingly, a 13-nucleotide sequence with perfect homology to the leader sequence is situated upstream of the suboptimal E TRS. Annealing of this 13-nucleotide sequence to the leader sequence may act as a compensatory mechanism for the disturbed leader-TRS/body-TRS interaction.

HCoV-229E. Human coronavirus 229E (HCoV-229E) is a single-stranded, positive-sense, RNA virus species in the *Alphacoronavirus* genus of the subfamily Coronavirinae, in the family Coronaviridae, of the order Nidovirales. Along with Human coronavirus OC43, it is responsible for the common cold. HCoV-NL63 and HCoV-229E are two of the four human coronaviruses that circulate worldwide. These two viruses are unique in their relationship towards each other. Phylogenetically, the viruses are more closely related to each other than to any other human coronavirus, yet they only share 65% sequence identity. Moreover, the viruses use different receptors to enter their target cell. HCoV-NL63 is associated with croup in children, whereas all signs suggest that the virus probably causes the common cold in healthy adults. HCoV-229E is a proven common cold virus in healthy adults, so it is probable that both viruses induce comparable symptoms in adults, even though their mode of infection differs (HCoV-NL63 and HCoV-229E are two of the four human coronaviruses that circulate worldwide. These two viruses are unique in their relationship towards each other. Phylogenetically, the viruses are more closely related to each other than to any other human coronavirus, yet they only share 65% sequence identity. Moreover, the viruses use different receptors to enter their target cell. HCoV-NL63 is associated with croup in children, whereas all signs suggest that the virus probably causes the common cold in healthy adults. HCoV-229E is a proven common cold virus in healthy adults, so it is probable that both viruses induce comparable symptoms in adults, even though their mode of infection differs (Dijkman R. et al. *J Formos Med Assoc.* 2009 April; 108(4):270-9, the contents of which is incorporated herein by reference in their entirety).

Combination Vaccines

Embodiments of the present disclosure also provide combination RNA (e.g., mRNA) vaccines. A "combination RNA (e.g., mRNA) vaccine" of the present disclosure refers to a vaccine comprising at least one (e.g., at least 2, 3, 4, or 5) RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a combination of any two or more (or all of) antigenic polypeptides selected from hMPV antigenic polypeptides, PIV3 antigenic polypeptides, RSV antigenic polypeptides, MeV antigenic polypeptides, and BetaCoV antigenic polypeptides (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a PIV3 antigenic polypeptide, a RSV antigenic polypeptide, a MeV antigenic polypeptide, and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide and a PIV3 antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide and a RSV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide and a MeV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide and a BetaCoV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a PIV3 antigenic polypeptide and a RSV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a PIV3 antigenic polypeptide and a MeV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a PIV3 antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a RSV antigenic polypeptide and a MeV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a RSV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a MeV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a PIV3 antigenic polypeptide, a RSV antigenic polypeptide and a MeV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a PIV3 antigenic polypeptide, a RSV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a PIV3 antigenic polypeptide, a MeV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a RSV antigenic polypeptide, a MeV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a PIV3 antigenic polypeptide, a RSV antigenic polypeptide, a MeV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a PIV3 antigenic polypeptide and a RSV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a PIV3 antigenic polypeptide and a MeV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a PIV3 antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a RSV antigenic polypeptide and a MeV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a RSV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a MeV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a PIV3 antigenic polypeptide, a RSV antigenic polypeptide and a MeV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a PIV3 antigenic polypeptide, a RSV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a RSV antigenic polypeptide, a MeV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

Other combination respiratory virus RNA (e.g., mRNA) vaccines are encompassed by the present disclosure.

It has been discovered that the mRNA vaccines described herein are superior to current vaccines in several ways. First, the lipid nanoparticle (LNP) delivery is superior to other formulations including a protamine base approach described in the literature and no additional adjuvants are to be necessary. The use of LNPs enables the effective delivery of chemically modified or unmodified mRNA vaccines. Additionally it has been demonstrated herein that both modified and unmodified LNP formulated mRNA vaccines were superior to conventional vaccines by a significant degree. In some embodiments the mRNA vaccines of the invention are superior to conventional vaccines by a factor of at least 10 fold, 20 fold, 40 fold, 50 fold, 100 fold, 500 fold or 1,000 fold.

Although attempts have been made to produce functional RNA vaccines, including mRNA vaccines and self-replicating RNA vaccines, the therapeutic efficacy of these RNA vaccines have not yet been fully established. Quite surprisingly, the inventors have discovered, according to aspects of the invention a class of formulations for delivering mRNA vaccines in vivo that results in significantly enhanced, and in many respects synergistic, immune responses including enhanced antigen generation and functional antibody production with neutralization capability. These results can be achieved even when significantly lower doses of the mRNA are administered in comparison with mRNA doses used in other classes of lipid based formulations. The formulations of the invention have demonstrated significant unexpected in vivo immune responses sufficient to establish the efficacy of functional mRNA vaccines as prophylactic and therapeutic agents. Additionally, self-replicating RNA vaccines rely on viral replication pathways to deliver enough RNA to a cell to produce an immunogenic response. The formulations of the invention do not require viral replication to produce enough protein to result in a strong immune response. Thus, the mRNA of the invention are not self-replicating RNA and do not include components necessary for viral replication.

The invention involves, in some aspects, the surprising finding that lipid nanoparticle (LNP) formulations significantly enhance the effectiveness of mRNA vaccines, including chemically modified and unmodified mRNA vaccines. The efficacy of mRNA vaccines formulated in LNP was examined in vivo using several distinct antigens. The results presented herein demonstrate the unexpected superior efficacy of the mRNA vaccines formulated in LNP over other commercially available vaccines.

In addition to providing an enhanced immune response, the formulations of the invention generate a more rapid immune response with fewer doses of antigen than other vaccines tested. The mRNA-LNP formulations of the invention also produce quantitatively and qualitatively better immune responses than vaccines formulated in a different carriers.

The data described herein demonstrate that the formulations of the invention produced significant unexpected improvements over existing antigen vaccines. Additionally, the mRNA-LNP formulations of the invention are superior to other vaccines even when the dose of mRNA is lower than other vaccines. Mice immunized with either 10 μg or 2 μg doses of an hMPV fusion protein mRNA LNP vaccine or a

PIV3 mRNA LNP vaccine produced neutralizing antibodies which for instance, successfully neutralized the hMPV B2 virus. A 10 μg dose of mRNA vaccine protected 100% of mice from lethal challenge and drastically reduced the viral titer after challenge (~2 log reduction).

Two 20 μg doses of MERS-CoV mRNA LNP vaccine significantly reduced viral load and induced significant amount of neutralizing antibodies against MERS-CoV (EC_{50} between 500-1000). The MERS-CoV mRNA vaccine induced antibody titer was 3-5 fold better than any other vaccines tested in the same model.

The LNP used in the studies described herein has been used previously to deliver siRNA in various animal models as well as in humans. In view of the observations made in association with the siRNA delivery of LNP formulations, the fact that LNP is useful in vaccines is quite surprising. It has been observed that therapeutic delivery of siRNA formulated in LNP causes an undesirable inflammatory response associated with a transient IgM response, typically leading to a reduction in antigen production and a compromised immune response. In contrast to the findings observed with siRNA, the LNP-mRNA formulations of the invention are demonstrated herein to generate enhanced IgG levels, sufficient for prophylactic and therapeutic methods rather than transient IgM responses.

Nucleic Acids/Polynucleotides

Respiratory virus vaccines, as provided herein, comprise at least one (one or more) ribonucleic acid (RNA) (e.g., mRNA) polynucleotide having an open reading frame encoding at least one antigenic polypeptide selected from hMPV, PIV3, RSV, MeV and BetaCoV (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1) antigenic polypeptides. The term "nucleic acid" includes any compound and/or substance that comprises a polymer of nucleotides (nucleotide monomer). These polymers are referred to as polynucleotides. Thus, the terms "nucleic acid" and "polynucleotide" are used interchangeably.

Nucleic acids may be or may include, for example, ribonucleic acids (RNAs), deoxyribonucleic acids (DNAs), threose nucleic acids (TNAs), glycol nucleic acids (GNAs), peptide nucleic acids (PNAs), locked nucleic acids (LNAs, including LNA having a β-D-ribo configuration, α-LNA having an α-L-ribo configuration (a diastereomer of LNA), 2'-amino-LNA having a 2'-amino functionalization, and 2'-amino-α-LNA having a 2'-amino functionalization), ethylene nucleic acids (ENA), cyclohexenyl nucleic acids (CeNA) or chimeras or combinations thereof.

In some embodiments, polynucleotides of the present disclosure function as messenger RNA (mRNA). "Messenger RNA" (mRNA) refers to any polynucleotide that encodes a (at least one) polypeptide (a naturally-occurring, non-naturally-occurring, or modified polymer of amino acids) and can be translated to produce the encoded polypeptide in vitro, in vivo, in situ or ex vivo. The skilled artisan will appreciate that, except where otherwise noted, polynucleotide sequences set forth in the instant application will recite "T"s in a representative DNA sequence but where the sequence represents RNA (e.g., mRNA), the "T"s would be substituted for "U"s. Thus, any of the RNA polynucleotides encoded by a DNA identified by a particular sequence identification number may also comprise the corresponding RNA (e.g., mRNA) sequence encoded by the DNA, where each "T" of the DNA sequence is substituted with "U."

The basic components of an mRNA molecule typically include at least one coding region, a 5' untranslated region (UTR), a 3' UTR, a 5' cap and a poly-A tail. Polynucleotides of the present disclosure may function as mRNA but can be distinguished from wild-type mRNA in their functional and/or structural design features, which serve to overcome existing problems of effective polypeptide expression using nucleic-acid based therapeutics.

In some embodiments, a RNA polynucleotide of an RNA (e.g., mRNA) vaccine encodes 2-10, 2-9, 2-8, 2-7, 2-6, 2-5, 2-4, 2-3, 3-10, 3-9, 3-8, 3-7, 3-6, 3-5, 3-4, 4-10, 4-9, 4-8, 4-7, 4-6, 4-5, 5-10, 5-9, 5-8, 5-7, 5-6, 6-10, 6-9, 6-8, 6-7, 7-10, 7-9, 7-8, 8-10, 8-9 or 9-10 antigenic polypeptides. In some embodiments, a RNA (e.g., mRNA) polynucleotide of a respiratory virus vaccine encodes at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 antigenic polypeptides. In some embodiments, a RNA (e.g., mRNA) polynucleotide of a respiratory virus vaccine encodes at least 100 or at least 200 antigenic polypeptides. In some embodiments, a RNA polynucleotide of an respiratory virus vaccine encodes 1-10, 5-15, 10-20, 15-25, 20-30, 25-35, 30-40, 35-45, 40-50, 1-50, 1-100, 2-50 or 2-100 antigenic polypeptides.

Polynucleotides of the present disclosure, in some embodiments, are codon optimized. Codon optimization methods are known in the art and may be used as provided herein. Codon optimization, in some embodiments, may be used to match codon frequencies in target and host organisms to ensure proper folding; bias GC content to increase mRNA stability or reduce secondary structures; minimize tandem repeat codons or base runs that may impair gene construction or expression; customize transcriptional and translational control regions; insert or remove protein trafficking sequences; remove/add post translation modification sites in encoded protein (e.g. glycosylation sites); add, remove or shuffle protein domains; insert or delete restriction sites; modify ribosome binding sites and mRNA degradation sites; adjust translational rates to allow the various domains of the protein to fold properly; or to reduce or eliminate problem secondary structures within the polynucleotide. Codon optimization tools, algorithms and services are known in the art—non-limiting examples include services from GeneArt (Life Technologies), DNA2.0 (Menlo Park Calif.) and/or proprietary methods. In some embodiments, the open reading frame (ORF) sequence is optimized using optimization algorithms.

In some embodiments, a codon optimized sequence shares less than 95% sequence identity, less than 90% sequence identity, less than 85% sequence identity, less than 80% sequence identity, or less than 75% sequence identity to a naturally-occurring or wild-type sequence (e.g., a naturally-occurring or wild-type mRNA sequence encoding a polypeptide or protein of interest (e.g., an antigenic protein or antigenic polypeptide)).

In some embodiments, a codon-optimized sequence shares between 65% and 85% (e.g., between about 67% and about 85%, or between about 67% and about 80%) sequence identity to a naturally-occurring sequence or a wild-type sequence (e.g., a naturally-occurring or wild-type mRNA sequence encoding a polypeptide or protein of interest (e.g., an antigenic protein or polypeptide)). In some embodiments, a codon-optimized sequence shares between 65% and 75%, or about 80% sequence identity to a naturally-occurring sequence or wild-type sequence (e.g., a naturally-occurring or wild-type mRNA sequence encoding a polypeptide or protein of interest (e.g., an antigenic protein or polypeptide)).

In some embodiments a codon-optimized RNA (e.g., mRNA) may, for instance, be one in which the levels of G/C are enhanced. The G/C-content of nucleic acid molecules may influence the stability of the RNA. RNA having an

increased amount of guanine (G) and/or cytosine (C) residues may be functionally more stable than nucleic acids containing a large amount of adenine (A) and thymine (T) or uracil (U) nucleotides. WO02/098443 discloses a pharmaceutical composition containing an mRNA stabilized by sequence modifications in the translated region. Due to the degeneracy of the genetic code, the modifications work by substituting existing codons for those that promote greater RNA stability without changing the resulting amino acid. The approach is limited to coding regions of the RNA.

Antigens/Antigenic Polypeptides

In some embodiments, an antigenic polypeptide (e.g., a hMPV, PIV3, RSV, MeV or BetaCoV antigenic polypeptide) is longer than 25 amino acids and shorter than 50 amino acids. Polypeptides include gene products, naturally occurring polypeptides, synthetic polypeptides, homologs, orthologs, paralogs, fragments and other equivalents, variants, and analogs of the foregoing. A polypeptide may be a single molecule or may be a multi-molecular complex such as a dimer, trimer or tetramer. Polypeptides may also comprise single chain polypeptides or multichain polypeptides, such as antibodies or insulin, and may be associated or linked to each other. Most commonly, disulfide linkages are found in multichain polypeptides. The term "polypeptide" may also apply to amino acid polymers in which at least one amino acid residue is an artificial chemical analogue of a corresponding naturally-occurring amino acid.

A "polypeptide variant" is a molecule that differs in its amino acid sequence relative to a native sequence or a reference sequence. Amino acid sequence variants may possess substitutions, deletions, insertions, or a combination of any two or three of the foregoing, at certain positions within the amino acid sequence, as compared to a native sequence or a reference sequence. Ordinarily, variants possess at least 50% identity to a native sequence or a reference sequence. In some embodiments, variants share at least 80% identity or at least 90% identity with a native sequence or a reference sequence.

In some embodiments "variant mimics" are provided. A "variant mimic" contains at least one amino acid that would mimic an activated sequence. For example, glutamate may serve as a mimic for phosphoro-threonine and/or phosphoroserine. Alternatively, variant mimics may result in deactivation or in an inactivated product containing the mimic. For example, phenylalanine may act as an inactivating substitution for tyrosine, or alanine may act as an inactivating substitution for serine.

"Orthologs" refers to genes in different species that evolved from a common ancestral gene by speciation. Normally, orthologs retain the same function in the course of evolution. Identification of orthologs is important for reliable prediction of gene function in newly sequenced genomes.

"Analogs" is meant to include polypeptide variants that differ by one or more amino acid alterations, for example, substitutions, additions or deletions of amino acid residues that still maintain one or more of the properties of the parent or starting polypeptide.

The present disclosure provides several types of compositions that are polynucleotide or polypeptide based, including variants and derivatives. These include, for example, substitutional, insertional, deletion and covalent variants and derivatives. The term "derivative" is synonymous with the term "variant" and generally refers to a molecule that has been modified and/or changed in any way relative to a reference molecule or a starting molecule.

As such, polynucleotides encoding peptides or polypeptides containing substitutions, insertions and/or additions, deletions and covalent modifications with respect to reference sequences, in particular the polypeptide sequences disclosed herein, are included within the scope of this disclosure. For example, sequence tags or amino acids, such as one or more lysines, can be added to peptide sequences (e.g., at the N-terminal or C-terminal ends). Sequence tags can be used for peptide detection, purification or localization. Lysines can be used to increase peptide solubility or to allow for biotinylation. Alternatively, amino acid residues located at the carboxy and amino terminal regions of the amino acid sequence of a peptide or protein may optionally be deleted providing for truncated sequences. Certain amino acids (e.g., C-terminal residues or N-terminal residues) alternatively may be deleted depending on the use of the sequence, as for example, expression of the sequence as part of a larger sequence that is soluble, or linked to a solid support.

"Substitutional variants" when referring to polypeptides are those that have at least one amino acid residue in a native or starting sequence removed and a different amino acid inserted in its place at the same position. Substitutions may be single, where only one amino acid in the molecule has been substituted, or they may be multiple, where two or more (e.g., 3, 4 or 5) amino acids have been substituted in the same molecule.

As used herein the term "conservative amino acid substitution" refers to the substitution of an amino acid that is normally present in the sequence with a different amino acid of similar size, charge, or polarity. Examples of conservative substitutions include the substitution of a non-polar (hydrophobic) residue such as isoleucine, valine and leucine for another non-polar residue. Likewise, examples of conservative substitutions include the substitution of one polar (hydrophilic) residue for another such as between arginine and lysine, between glutamine and asparagine, and between glycine and serine. Additionally, the substitution of a basic residue such as lysine, arginine or histidine for another, or the substitution of one acidic residue such as aspartic acid or glutamic acid for another acidic residue are additional examples of conservative substitutions. Examples of non-conservative substitutions include the substitution of a non-polar (hydrophobic) amino acid residue such as isoleucine, valine, leucine, alanine, methionine for a polar (hydrophilic) residue such as cysteine, glutamine, glutamic acid or lysine and/or a polar residue for a non-polar residue.

"Features" when referring to polypeptide or polynucleotide are defined as distinct amino acid sequence-based or nucleotide-based components of a molecule respectively. Features of the polypeptides encoded by the polynucleotides include surface manifestations, local conformational shape, folds, loops, half-loops, domains, half-domains, sites, termini and any combination(s) thereof.

As used herein when referring to polypeptides the term "domain" refers to a motif of a polypeptide having one or more identifiable structural or functional characteristics or properties (e.g., binding capacity, serving as a site for protein-protein interactions).

As used herein when referring to polypeptides the terms "site" as it pertains to amino acid based embodiments is used synonymously with "amino acid residue" and "amino acid side chain." As used herein when referring to polynucleotides the terms "site" as it pertains to nucleotide based embodiments is used synonymously with "nucleotide." A site represents a position within a peptide or polypeptide or

polynucleotide that may be modified, manipulated, altered, derivatized or varied within the polypeptide-based or polynucleotide-based molecules.

As used herein the terms "termini" or "terminus" when referring to polypeptides or polynucleotides refers to an extremity of a polypeptide or polynucleotide respectively. Such extremity is not limited only to the first or final site of the polypeptide or polynucleotide but may include additional amino acids or nucleotides in the terminal regions. Polypeptide-based molecules may be characterized as having both an N-terminus (terminated by an amino acid with a free amino group (NH2)) and a C-terminus (terminated by an amino acid with a free carboxyl group (COOH)). Proteins are in some cases made up of multiple polypeptide chains brought together by disulfide bonds or by non-covalent forces (multimers, oligomers). These proteins have multiple N- and C-termini. Alternatively, the termini of the polypeptides may be modified such that they begin or end, as the case may be, with a non-polypeptide based moiety such as an organic conjugate.

As recognized by those skilled in the art, protein fragments, functional protein domains, and homologous proteins are also considered to be within the scope of polypeptides of interest. For example, provided herein is any protein fragment (meaning a polypeptide sequence at least one amino acid residue shorter than a reference polypeptide sequence but otherwise identical) of a reference protein having a length of 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or longer than 100 amino acids. In another example, any protein that includes a stretch of 20, 30, 40, 50, or 100 (contiguous) amino acids that are 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% identical to any of the sequences described herein can be utilized in accordance with the disclosure. In some embodiments, a polypeptide includes 2, 3, 4, 5, 6, 7, 8, 9, 10, or more mutations as shown in any of the sequences provided herein or referenced herein. In another example, any protein that includes a stretch of 20, 30, 40, 50, or 100 amino acids that are greater than 80%, 90%, 95%, or 100% identical to any of the sequences described herein, wherein the protein has a stretch of 5, 10, 15, 20, 25, or 30 amino acids that are less than 80%, 75%, 70%, 65% to 60% identical to any of the sequences described herein can be utilized in accordance with the disclosure.

Polypeptide or polynucleotide molecules of the present disclosure may share a certain degree of sequence similarity or identity with the reference molecules (e.g., reference polypeptides or reference polynucleotides), for example, with art-described molecules (e.g., engineered or designed molecules or wild-type molecules). The term "identity," as known in the art, refers to a relationship between the sequences of two or more polypeptides or polynucleotides, as determined by comparing the sequences. In the art, identity also means the degree of sequence relatedness between two sequences as determined by the number of matches between strings of two or more amino acid residues or nucleic acid residues. Identity measures the percent of identical matches between the smaller of two or more sequences with gap alignments (if any) addressed by a particular mathematical model or computer program (e.g., "algorithms"). Identity of related peptides can be readily calculated by known methods. "% identity" as it applies to polypeptide or polynucleotide sequences is defined as the percentage of residues (amino acid residues or nucleic acid residues) in the candidate amino acid or nucleic acid sequence that are identical with the residues in the amino acid sequence or nucleic acid sequence of a second sequence after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent identity. Methods and computer programs for the alignment are well known in the art. Identity depends on a calculation of percent identity but may differ in value due to gaps and penalties introduced in the calculation. Generally, variants of a particular polynucleotide or polypeptide have at least 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% but less than 100% sequence identity to that particular reference polynucleotide or polypeptide as determined by sequence alignment programs and parameters described herein and known to those skilled in the art. Such tools for alignment include those of the BLAST suite (Stephen F. Altschul, et al. (1997)." Gapped BLAST and PSI-BLAST: a new generation of protein database search programs," *Nucleic Acids Res.* 25:3389-3402). Another popular local alignment technique is based on the Smith-Waterman algorithm (Smith, T. F. & Waterman, M. S. (1981) "Identification of common molecular subsequences." *J. Mol. Biol.* 147:195-197). A general global alignment technique based on dynamic programming is the Needleman-Wunsch algorithm (Needleman, S. B. & Wunsch, C. D. (1970) "A general method applicable to the search for similarities in the amino acid sequences of two proteins." *J. Mol. Biol.* 48:443-453). More recently, a Fast Optimal Global Sequence Alignment Algorithm (FOGSAA) was developed that purportedly produces global alignment of nucleotide and protein sequences faster than other optimal global alignment methods, including the Needleman-Wunsch algorithm. Other tools are described herein, specifically in the definition of "identity" below.

As used herein, the term "homology" refers to the overall relatedness between polymeric molecules, e.g. between nucleic acid molecules (e.g. DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Polymeric molecules (e.g. nucleic acid molecules (e.g. DNA molecules and/or RNA molecules) and/or polypeptide molecules) that share a threshold level of similarity or identity determined by alignment of matching residues are termed homologous. Homology is a qualitative term that describes a relationship between molecules and can be based upon the quantitative similarity or identity. Similarity or identity is a quantitative term that defines the degree of sequence match between two compared sequences. In some embodiments, polymeric molecules are considered to be "homologous" to one another if their sequences are at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical or similar. The term "homologous" necessarily refers to a comparison between at least two sequences (polynucleotide or polypeptide sequences). Two polynucleotide sequences are considered homologous if the polypeptides they encode are at least 50%, 60%, 70%, 80%, 90%, 95%, or even 99% for at least one stretch of at least 20 amino acids. In some embodiments, homologous polynucleotide sequences are characterized by the ability to encode a stretch of at least 4-5 uniquely specified amino acids. For polynucleotide sequences less than 60 nucleotides in length, homology is determined by the ability to encode a stretch of at least 4-5 uniquely specified amino acids. Two protein sequences are considered homologous if the proteins are at least 50%, 60%, 70%, 80%, or 90% identical for at least one stretch of at least 20 amino acids.

Homology implies that the compared sequences diverged in evolution from a common origin. The term "homolog" refers to a first amino acid sequence or nucleic acid sequence (e.g., gene (DNA or RNA) or protein sequence) that is related to a second amino acid sequence or nucleic acid sequence by descent from a common ancestral sequence.

The term "homolog" may apply to the relationship between genes and/or proteins separated by the event of speciation or to the relationship between genes and/or proteins separated by the event of genetic duplication. "Orthologs" are genes (or proteins) in different species that evolved from a common ancestral gene (or protein) by speciation. Typically, orthologs retain the same function in the course of evolution. "Paralogs" are genes (or proteins) related by duplication within a genome. Orthologs retain the same function in the course of evolution, whereas paralogs evolve new functions, even if these are related to the original one.

The term "identity" refers to the overall relatedness between polymeric molecules, for example, between polynucleotide molecules (e.g. DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of the percent identity of two polynucleic acid sequences, for example, can be performed by aligning the two sequences for optimal comparison purposes (e.g., gaps can be introduced in one or both of a first and a second nucleic acid sequences for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or 100% of the length of the reference sequence. The nucleotides at corresponding nucleotide positions are then compared. When a position in the first sequence is occupied by the same nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which needs to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. For example, the percent identity between two nucleic acid sequences can be determined using methods such as those described in Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; Computer Analysis of Sequence Data, Part I, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; each of which is incorporated herein by reference. For example, the percent identity between two nucleic acid sequences can be determined using the algorithm of Meyers and Miller (CABIOS, 1989, 4:11-17), which has been incorporated into the ALIGN program (version 2.0) using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. The percent identity between two nucleic acid sequences can, alternatively, be determined using the GAP program in the GCG software package using an NWSgapdna.CMP matrix. Methods commonly employed to determine percent identity between sequences include, but are not limited to those disclosed in Carillo, H., and Lipman, D., SIAM *J Applied Math.,* 48:1073 (1988); incorporated herein by reference. Techniques for determining identity are codified in publicly available computer programs. Exemplary computer software to determine homology between two sequences include, but are not limited to, GCG program package, Devereux, J., et al., *Nucleic Acids Research,* 12(1), 387 (1984)), BLASTP, BLASTN, and FASTA Altschul, S. F. et al., *J. Molec. Biol.,* 215, 403 (1990)).

Multiprotein and Multicomponent Vaccines

The present disclosure encompasses respiratory virus vaccines comprising multiple RNA (e.g., mRNA) polynucleotides, each encoding a single antigenic polypeptide, as well as respiratory virus vaccines comprising a single RNA polynucleotide encoding more than one antigenic polypeptide (e.g., as a fusion polypeptide). Thus, a vaccine composition comprising a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a first antigenic polypeptide and a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a second antigenic polypeptide encompasses (a) vaccines that comprise a first RNA polynucleotide encoding a first antigenic polypeptide and a second RNA polynucleotide encoding a second antigenic polypeptide, and (b) vaccines that comprise a single RNA polynucleotide encoding a first and second antigenic polypeptide (e.g., as a fusion polypeptide). RNA (e.g., mRNA) vaccines of the present disclosure, in some embodiments, comprise 2-10 (e.g., 2, 3, 4, 5, 6, 7, 8, 9 or 10), or more, RNA polynucleotides having an open reading frame, each of which encodes a different antigenic polypeptide (or a single RNA polynucleotide encoding 2-10, or more, different antigenic polypeptides). The antigenic polypeptides may be selected from hMPV, PIV3, RSV, MEV and BetaCoV (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1) antigenic polypeptides.

In some embodiments, a respiratory virus vaccine comprises a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a viral capsid protein, a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a viral premembrane/membrane protein, and a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a viral envelope protein. In some embodiments, a respiratory virus vaccine comprises a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a viral fusion (F) protein and a RNA polynucleotide having an open reading frame encoding a viral major surface glycoprotein (G protein). In some embodiments, a vaccine comprises a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a viral F protein. In some embodiments, a vaccine comprises a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a viral G protein. In some embodiments, a vaccine comprises a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a HN protein.

In some embodiments, a multicomponent vaccine comprises at least one RNA (e.g., mRNA) polynucleotide encoding at least one antigenic polypeptide fused to a signal peptide (e.g., any one of SEQ ID NO: 15-19). The signal peptide may be fused at the N-terminus or the C-terminus of an antigenic polypeptide. An antigenic polypeptide fused to a signal peptide may be selected from hMPV, PIV3, RSV, MEV and BetaCoV (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1) antigenic polypeptides.

Signal Peptides

In some embodiments, antigenic polypeptides encoded by respiratory virus RNA (e.g., mRNA) polynucleotides comprise a signal peptide. Signal peptides, comprising the N-terminal 15-60 amino acids of proteins, are typically needed for the translocation across the membrane on the secretory pathway and, thus, universally control the entry of most proteins both in eukaryotes and prokaryotes to the secretory pathway. Signal peptides generally include three

regions: an N-terminal region of differing length, which usually comprises positively charged amino acids; a hydrophobic region; and a short carboxy-terminal peptide region. In eukaryotes, the signal peptide of a nascent precursor protein (pre-protein) directs the ribosome to the rough endoplasmic reticulum (ER) membrane and initiates the transport of the growing peptide chain across it for processing. ER processing produces mature proteins, wherein the signal peptide is cleaved from precursor proteins, typically by a ER-resident signal peptidase of the host cell, or they remain uncleaved and function as a membrane anchor. A signal peptide may also facilitate the targeting of the protein to the cell membrane. The signal peptide, however, is not responsible for the final destination of the mature protein. Secretory proteins devoid of additional address tags in their sequence are by default secreted to the external environment. During recent years, a more advanced view of signal peptides has evolved, showing that the functions and immunodominance of certain signal peptides are much more versatile than previously anticipated.

Respiratory virus vaccines of the present disclosure may comprise, for example, RNA (e.g., mRNA) polynucleotides encoding an artificial signal peptide, wherein the signal peptide coding sequence is operably linked to and is in frame with the coding sequence of the antigenic polypeptide. Thus, respiratory virus vaccines of the present disclosure, in some embodiments, produce an antigenic polypeptide comprising an antigenic polypeptide (e.g., hMPV, PIV3, RSV, MeV or BetaCoV) fused to a signal peptide. In some embodiments, a signal peptide is fused to the N-terminus of the antigenic polypeptide. In some embodiments, a signal peptide is fused to the C-terminus of the antigenic polypeptide.

In some embodiments, the signal peptide fused to the antigenic polypeptide is an artificial signal peptide. In some embodiments, an artificial signal peptide fused to the antigenic polypeptide encoded by the RNA (e.g., mRNA) vaccine is obtained from an immunoglobulin protein, e.g., an IgE signal peptide or an IgG signal peptide. In some embodiments, a signal peptide fused to the antigenic polypeptide encoded by a RNA (e.g., mRNA) vaccine is an Ig heavy chain epsilon-1 signal peptide (IgE HC SP) having the sequence of: MDWTWILFLVAAATRVHS (SEQ ID NO: 16). In some embodiments, a signal peptide fused to the antigenic polypeptide encoded by the (e.g., mRNA) RNA (e.g., mRNA) vaccine is an IgGk chain V-III region HAH signal peptide (IgGk SP) having the sequence of METPAQLLFLLLLWLPDTTG (SEQ ID NO: 15). In some embodiments, the signal peptide is selected from: Japanese encephalitis PRM signal sequence (MLGSNSGQRVVFTILLLLVAPAYS; SEQ ID NO: 17), VSVg protein signal sequence (MKCLLYLAFLFIGVNCA; SEQ ID NO: 18) and Japanese encephalitis JEV signal sequence (MWLVSLAIVTACAGA; SEQ ID NO: 19).

In some embodiments, the antigenic polypeptide encoded by a RNA (e.g., mRNA) vaccine comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, 47-50 or 54-56 (Tables 3, 6, 11, 14 or 17; see also amino acid sequences of Tables 4, 7, 12 or 15) fused to a signal peptide identified by any one of SEQ ID NO: 15-19 (Table 8). The examples disclosed herein are not meant to be limiting and any signal peptide that is known in the art to facilitate targeting of a protein to ER for processing and/or targeting of a protein to the cell membrane may be used in accordance with the present disclosure.

A signal peptide may have a length of 15-60 amino acids. For example, a signal peptide may have a length of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, or 60 amino acids. In some embodiments, a signal peptide has a length of 20-60, 25-60, 30-60, 35-60, 40-60, 45-60, 50-60, 55-60, 15-55, 20-55, 25-55, 30-55, 35-55, 40-55, 45-55, 50-55, 15-50, 20-50, 25-50, 30-50, 35-50, 40-50, 45-50, 15-45, 20-45, 25-45, 30-45, 35-45, 40-45, 15-40, 20-40, 25-40, 30-40, 35-40, 15-35, 20-35, 25-35, 30-35, 15-30, 20-30, 25-30, 15-25, 20-25, or 15-20 amino acids.

A signal peptide is typically cleaved from the nascent polypeptide at the cleavage junction during ER processing. The mature antigenic polypeptide produce by a respiratory virus RNA (e.g., mRNA) vaccine of the present disclosure typically does not comprise a signal peptide.

Chemical Modifications

Respiratory virus vaccines of the present disclosure, in some embodiments, comprise at least RNA (e.g. mRNA) polynucleotide having an open reading frame encoding at least one antigenic polypeptide that comprises at least one chemical modification.

The terms "chemical modification" and "chemically modified" refer to modification with respect to adenosine (A), guanosine (G), uridine (U), thymidine (T) or cytidine (C) ribonucleosides or deoxyribnucleosides in at least one of their position, pattern, percent or population. Generally, these terms do not refer to the ribonucleotide modifications in naturally occurring 5'-terminal mRNA cap moieties. With respect to a polypeptide, the term "modification" refers to a modification relative to the canonical set 20 amino acids. Polypeptides, as provided herein, are also considered "modified" of they contain amino acid substitutions, insertions or a combination of substitutions and insertions.

Polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides), in some embodiments, comprise various (more than one) different modifications. In some embodiments, a particular region of a polynucleotide contains one, two or more (optionally different) nucleoside or nucleotide modifications. In some embodiments, a modified RNA polynucleotide (e.g., a modified mRNA polynucleotide), introduced to a cell or organism, exhibits reduced degradation in the cell or organism, respectively, relative to an unmodified polynucleotide. In some embodiments, a modified RNA polynucleotide (e.g., a modified mRNA polynucleotide), introduced into a cell or organism, may exhibit reduced immunogenicity in the cell or organism, respectively (e.g., a reduced innate response).

Modifications of polynucleotides include, without limitation, those described herein. Polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) may comprise modifications that are naturally-occurring, non-naturally-occurring or the polynucleotide may comprise a combination of naturally-occurring and non-naturally-occurring modifications. Polynucleotides may include any useful modification, for example, of a sugar, a nucleobase, or an internucleoside linkage (e.g., to a linking phosphate, to a phosphodiester linkage or to the phosphodiester backbone).

Polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides), in some embodiments, comprise non-natural modified nucleotides that are introduced during synthesis or post-synthesis of the polynucleotides to achieve desired functions or properties. The modifications may be present on an internucleotide linkages, purine or pyrimidine bases, or sugars. The modification may be introduced with chemical synthesis or with a polymerase enzyme at the terminal of a chain or anywhere else in the chain. Any of the regions of a polynucleotide may be chemically modified.

The present disclosure provides for modified nucleosides and nucleotides of a polynucleotide (e.g., RNA polynucleotides, such as mRNA polynucleotides). A "nucleoside" refers to a compound containing a sugar molecule (e.g., a pentose or ribose) or a derivative thereof in combination with an organic base (e.g., a purine or pyrimidine) or a derivative thereof (also referred to herein as "nucleobase"). A nucleotide" refers to a nucleoside, including a phosphate group. Modified nucleotides may by synthesized by any useful method, such as, for example, chemically, enzymatically, or recombinantly, to include one or more modified or non-natural nucleosides. Polynucleotides may comprise a region or regions of linked nucleosides. Such regions may have variable backbone linkages. The linkages may be standard phosphdioester linkages, in which case the polynucleotides would comprise regions of nucleotides.

Modified nucleotide base pairing encompasses not only the standard adenosine-thymine, adenosine-uracil, or guanosine-cytosine base pairs, but also base pairs formed between nucleotides and/or modified nucleotides comprising non-standard or modified bases, wherein the arrangement of hydrogen bond donors and hydrogen bond acceptors permits hydrogen bonding between a non-standard base and a standard base or between two complementary non-standard base structures. One example of such non-standard base pairing is the base pairing between the modified nucleotide inosine and adenine, cytosine or uracil. Any combination of base/sugar or linker may be incorporated into polynucleotides of the present disclosure.

Modifications of polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) that are useful in the vaccines of the present disclosure include, but are not limited to the following: 2-methylthio-N6-(cis-hydroxyisopentenyl)adenosine; 2-methylthio-N6-methyladenosine; 2-methylthio-N6-threonyl carbamoyladenosine; N6-glycinylcarbamoyladenosine; N6-isopentenyladenosine; N6-methyladenosine; N6-threonylcarbamoyladeno sine; 1,2'-O-dimethyladenosine; 1-methyladenosine; 2'-O-methyladenosine; 2'-O-ribosyladenosine (phosphate); 2-methyladenosine; 2-methylthio-N6 isopentenyladenosine; 2-methylthio-N6-hydroxynorvalyl carbamoyladenosine; 2'-O-methyladenosine; 2'-O-ribosyladenosine (phosphate); Isopentenyladenosine; N6-(cis-hydroxyisopentenyl)adenosine; N6,2'-O-dimethyladenosine; N6,2'-O-dimethyladenosine; N6,N6,2'-O-trimethyladenosine; N6,N6-dimethyladenosine; N6-acetyladenosine; N6-hydroxynorvalylcarbamoyladenosine; N6-methyl-N6-threonylcarbamoyladenosine; 2-methyladenosine; 2-methylthio-N6-isopentenyladenosine; 7-deaza-adenosine; N1-methyl-adenosine; N6,N6 (dimethyl)adenine; N6-cis-hydroxy-isopentenyl-adenosine; α-thio-adenosine; 2 (amino)adenine; 2 (aminopropyl)adenine; 2 (methylthio) N6 (isopentenyl)adenine; 2-(alkyl)adenine; 2-(aminoalkyl)adenine; 2-(aminopropyl)adenine; 2-(halo)adenine; 2-(halo) adenine; 2-(propyl)adenine; 2'-Amino-2'-deoxy-ATP; 2'-Azido-2'-deoxy-ATP; 2'-Deoxy-2'-a-aminoadenosine TP; 2'-Deoxy-2'-a-azidoadenosine TP; 6 (alkyl)adenine; 6 (methyl)adenine; 6-(alkyl)adenine; 6-(methyl)adenine; 7 (deaza)adenine; 8 (alkenyl)adenine; 8 (alkynyl)adenine; 8 (amino)adenine; 8 (thioalkyl)adenine; 8-(alkenyl)adenine; 8-(alkyl)adenine; 8-(alkynyl)adenine; 8-(amino)adenine; 8-(halo)adenine; 8-(hydroxyl)adenine; 8-(thioalkyl)adenine; 8-(thiol)adenine; 8-azido-adeno sine; aza adenine; deaza adenine; N6 (methyl)adenine; N6-(isopentyl)adenine; 7-deaza-8-aza-adenosine; 7-methyladenine; 1-Deazaadenosine TP; 2'Fluoro-N6-Bz-deoxyadenosine TP; 2'-OMe-2-Amino-ATP; 2'O-methyl-N6-Bz-deoxyadenosine TP; 2'-a-Ethynyladenosine TP; 2-aminoadenine; 2-Aminoadenosine TP; 2-Amino-ATP; 2'-a-Trifluoromethyladenosine TP; 2-Azidoadenosine TP; 2'-b-Ethynyladenosine TP; 2-Bromoadenosine TP; 2'-b-Trifluoromethyladenosine TP; 2-Chloroadenosine TP; 2'-Deoxy-2',2'-difluoroadenosine TP; 2'-Deoxy-2'-a-mercaptoadenosine TP; 2'-Deoxy-2'-a-thiomethoxyadenosine TP; 2'-Deoxy-2'-b-aminoadenosine TP; 2'-Deoxy-2'-b-azidoadenosine TP; 2'-Deoxy-2'-b-bromoadenosine TP; 2'-Deoxy-2'-b-chloroadenosine TP; 2'-Deoxy-2'-b-fluoroadenosine TP; 2'-Deoxy-2'-b-iodoadenosine TP; 2'-Deoxy-2'-b-mercaptoadenosine TP; 2'-Deoxy-2'-b-thiomethoxyadenosine TP; 2-Fluoroadenosine TP; 2-Iodoadenosine TP; 2-Mercaptoadenosine TP; 2-methoxy-adenine; 2-methylthio-adenine; 2-Trifluoromethyladenosine TP; 3-Deaza-3-bromoadenosine TP; 3-Deaza-3-chloroadenosine TP; 3-Deaza-3-fluoroadenosine TP; 3-Deaza-3-iodoadenosine TP; 3-Deazaadenosine TP; 4'-Azidoadenosine TP; 4'-Carbocyclic adenosine TP; 4'-Ethynyladenosine TP; 5'-Homo-adenosine TP; 8-Aza-ATP; 8-bromo-adenosine TP; 8-Trifluoromethyladenosine TP; 9-Deazaadenosine TP; 2-aminopurine; 7-deaza-2,6-diaminopurine; 7-deaza-8-aza-2,6-diaminopurine; 7-deaza-8-aza-2-aminopurine; 2,6-diaminopurine; 7-deaza-8-aza-adenine, 7-deaza-2-aminopurine; 2-thiocytidine; 3-methylcytidine; 5-formylcytidine; 5-hydroxymethylcytidine; 5-methylcytidine; N4-acetylcytidine; 2'-O-methylcytidine; 2'-O-methylcytidine; 5,2'-O-dimethylcytidine; 5-formyl-2'-O-methylcytidine; Lysidine; N4,2'-O-dimethylcytidine; N4-acetyl-2'-O-methylcytidine; N4-methylcytidine; N4,N4-Dimethyl-2'-OMe-Cytidine TP; 4-methylcytidine; 5-aza-cytidine; Pseudo-iso-cytidine; pyrrolo-cytidine; α-thio-cytidine; 2-(thio)cytosine; 2'-Amino-2'-deoxy-CTP; 2'-Azido-2'-deoxy-CTP; 2'-Deoxy-2'-a-aminocytidine TP; 2'-Deoxy-2'-a-azidocytidine TP; 3 (deaza) 5 (aza)cytosine; 3 (methyl)cytosine; 3-(alkyl)cytosine; 3-(deaza) 5 (aza)cytosine; 3-(methyl)cytidine; 4,2'-O-dimethylcytidine; 5 (halo)cytosine; 5 (methyl)cytosine; 5 (propynyl)cytosine; 5 (trifluoromethyl)cytosine; 5-(alkyl)cytosine; 5-(alkynyl)cytosine; 5-(halo)cytosine; 5-(propynyl) cytosine; 5-(trifluoromethyl)cytosine; 5-bromo-cytidine; 5-iodo-cytidine; 5-propynyl cytosine; 6-(azo)cytosine; 6-aza-cytidine; aza cytosine; deaza cytosine; N4 (acetyl) cytosine; 1-methyl-1-deaza-pseudoisocytidine; 1-methyl-pseudoisocytidine; 2-methoxy-5-methyl-cytidine; 2-methoxy-cytidine; 2-thio-5-methyl-cytidine; 4-methoxy-1-methyl-pseudoisocytidine; 4-methoxy-pseudoisocytidine; 4-thio-1-methyl-1-deaza-pseudoisocytidine; 4-thio-1-methyl-pseudoisocytidine; 4-thio-pseudoisocytidine; 5-aza-zebularine; 5-methyl-zebularine; pyrrolo-pseudoisocytidine; Zebularine; (E)-5-(2-Bromo-vinyl)cytidine TP; 2,2'-anhydro-cytidine TP hydrochloride; 2'Fluor-N4-Bz-cytidine TP; 2'Fluoro-N4-Acetyl-cytidine TP; 2'-O-Methyl-N4-Acetyl-cytidine TP; 2'O-methyl-N4-Bz-cytidine TP; 2'-a-Ethynylcytidine TP; 2'-a-Trifluoromethylcytidine TP; 2'-b-Ethynylcytidine TP; 2'-b-Trifluoromethylcytidine TP; 2'-Deoxy-2',2'-difluorocytidine TP; 2'-Deoxy-2'-a-mercaptocytidine TP; 2'-Deoxy-2'-a-thiomethoxycytidine TP; 2'-Deoxy-2'-b-aminocytidine TP; 2'-Deoxy-2'-b-azidocytidine TP; 2'-Deoxy-2'-b-bromocytidine TP; 2'-Deoxy-2'-b-chlorocytidine TP; 2'-Deoxy-2'-b-fluorocytidine TP; 2'-Deoxy-2'-b-iodocytidine TP; 2'-Deoxy-2'-b-mercaptocytidine TP; 2'-Deoxy-2'-b-thiomethoxycytidine TP; 2'-O-Methyl-5-(1-propynyl)cytidine TP; 3'-Ethynylcytidine TP; 4'-Azidocytidine TP; 4'-Carbocyclic cytidine TP; 4'-Ethynylcytidine TP; 5-(1-Propynyl)ara-cytidine TP; 5-(2-Chloro-phenyl)-2-thiocytidine TP; 5-(4-Amino-phenyl)-2-thiocytidine TP; 5-Aminoallyl-CTP; 5-Cyanocytidine TP; 5-Ethynylara-cytidine TP; 5-Ethynylcytidine TP; 5'-Homo-cytidine TP;

5-Methoxycytidine TP; 5-Trifluoromethyl-Cytidine TP; N4-Amino-cytidine TP; N4-Benzoyl-cytidine TP; Pseudoisocytidine; 7-methylguanosine; N2,2'-O-dimethylguanosine; N2-methylguanosine; Wyosine; 1,2'-O-dimethylguanosine; 1-methylguanosine; 2'-O-methylguanosine; 2'-O-ribosylguanosine (phosphate); 2'-O-methylguanosine; 2'-O-ribosylguanosine (phosphate); 7-aminomethyl-7-deazaguanosine; 7-cyano-7-deazaguanosine; Archaeosine; Methylwyo sine; N2,7-dimethylguanosine; N2,N2,2'-O-trimethylguanosine; N2,N2,7-trimethylguanosine; N2,N2-dimethylguanosine; N2,7,2'-O-trimethylguanosine; 6-thioguanosine; 7-deaza-guanosine; 8-oxo-guanosine; N1-methyl-guanosine; α-thio-guanosine; 2 (propyl)guanine; 2-(alkyl)guanine; 2'-Amino-2'-deoxy-GTP; 2'-Azido-2'-deoxy-GTP; 2'-Deoxy-2'-a-aminoguanosine TP; 2'-Deoxy-2'-a-azidoguanosine TP; 6 (methyl)guanine; 6-(alkyl)guanine; 6-(methyl)guanine; 6-methyl-guanosine; 7 (alkyl)guanine; 7 (deaza)guanine; 7 (methyl)guanine; 7-(alkyl)guanine; 7-(deaza)guanine; 7-(methyl)guanine; 8 (alkyl)guanine; 8 (alkynyl)guanine; 8 (halo)guanine; 8 (thioalkyl)guanine; 8-(alkenyl)guanine; 8-(alkyl)guanine; 8-(alkynyl)guanine; 8-(amino)guanine; 8-(halo)guanine; 8-(hydroxyl)guanine; 8-(thioalkyl)guanine; 8-(thiol)guanine; aza guanine; deaza guanine; N (methyl)guanine; N-(methyl)guanine; 1-methyl-6-thio-guanosine; 6-methoxy-guanosine; 6-thio-7-deaza-8-aza-guanosine; 6-thio-7-deaza-guanosine; 6-thio-7-methyl-guanosine; 7-deaza-8-aza-guanosine; 7-methyl-8-oxo-guanosine; N2,N2-dimethyl-6-thio-guanosine; N2-methyl-6-thio-guanosine; 1-Me-GTP; 2'Fluoro-N2-isobutyl-guanosine TP; 2'O-methyl-N2-isobutyl-guanosine TP; 2'-a-Ethynylguanosine TP; 2'-a-Trifluoromethylguanosine TP; 2'-b-Ethynylguano sine TP; 2'-b-Trifluoromethylguanosine TP; 2'-Deoxy-2',2'-difluoroguanosine TP; 2'-Deoxy-2'-a-mercaptoguanosine TP; 2'-Deoxy-2'-a-thiomethoxyguanosine TP; 2'-Deoxy-2'-b-aminoguanosine TP; 2'-Deoxy-2'-b-azidoguanosine TP; 2'-Deoxy-2'-b-bromoguanosine TP; 2'-Deoxy-2'-b-chloroguanosine TP; 2'-Deoxy-2'-b-fluoroguanosine TP; 2'-Deoxy-2'-b-iodoguanosine TP; 2'-Deoxy-2'-b-mercaptoguanosine TP; 2'-Deoxy-2'-b-thiomethoxyguanosine TP; 4'-Azidoguanosine TP; 4'-Carbocyclic guanosine TP; 4'-Ethynylguanosine TP; 5'-Homo-guanosine TP; 8-bromo-guanosine TP; 9-Deaza-guanosine TP; N2-isobutyl-guanosine TP; 1-methylinosine; Inosine; 1,2'-O-dimethylinosine; 2'-O-methylinosine; 7-methylinosine; 2'-O-methylinosine; Epoxyqueuosine; galactosyl-queuosine; Mannosylqueuosine; Queuosine; allyamino-thymidine; aza thymidine; deaza thymidine; deoxy-thymidine; 2'-O-methyluridine; 2-thiouridine; 3-methyluridine; 5-carboxymethyluridine; 5-hydroxyuridine; 5-methyluridine; 5-taurinomethyl-2-thiouridine; 5-taurinomethyluridine; Dihydrouridine; Pseudouridine; (3-(3-amino-3-carboxypropyl)uridine; 1-methyl-3-(3-amino-5-carboxypropyl)pseudouridine; 1-methylpseduouridine; 1-methyl-pseudouridine; 2'-O-methyluridine; 2'-O-methylpseudouridine; 2'-O-methyluridine; 2-thio-2'-O-methyluridine; 3-(3-amino-3-carboxypropyl)uridine; 3,2'-O-dimethyluridine; 3-Methyl-pseudo-Uridine TP; 4-thiouridine; 5-(carboxyhydroxymethyl)uridine; 5-(carboxyhydroxymethyl)uridine methyl ester; 5,2'-O-dimethyluridine; 5,6-dihydro-uridine; 5-aminomethyl-2-thiouridine; 5-carbamoylmethyl-2'-O-methyluridine; 5-carbamoylmethyluridine; 5-carboxyhydroxymethyluridine; 5-carboxyhydroxymethyluridine methyl ester; 5-carboxymethylaminomethyl-2'-O-methyluridine; 5-carboxymethylaminomethyl-2-thiouridine; 5-carboxymethylaminomethyl-2-thiouridine; 5-carboxymethylaminomethyluridine; 5-carboxymethylaminomethyluridine; 5-Carbamoylmethyluridine TP; 5-methoxycarbonylmethyl-2'-O-methyluridine; 5-methoxycarbonylmethyl-2-thiouridine; 5-methoxycarbonylmethyluridine; 5-methoxyuridine; 5-methyl-2-thiouridine; 5-methylaminomethyl-2-selenouridine; 5-methylaminomethyl-2-thiouridine; 5-methylaminomethyluridine; 5-Methyldihydrouridine; 5-Oxyacetic acid-Uridine TP; 5-Oxyacetic acid-methyl ester-Uridine TP; N1-methyl-pseudo-uridine; uridine 5-oxyacetic acid; uridine 5-oxyacetic acid methyl ester; 3-(3-Amino-3-carboxypropyl)-Uridine TP; 5-(iso-Pentenylaminomethyl)-2-thiouridine TP; 5-(iso-Pentenylaminomethyl)-2'-O-methyluridine TP; 5-(iso-Pentenylaminomethyl)uridine TP; 5-propynyl uracil; α-thio-uridine; 1 (aminoalkylamino-carbonylethylenyl)-2 (thio)-pseudouracil; 1 (aminoalkylaminocarbonylethylenyl)-2,4-(dithio)pseudouracil; 1 (aminoalkylaminocarbonylethylenyl)-4 (thio)pseudouracil; 1 (aminoalkylaminocarbonylethylenyl)-pseudouracil; 1 (aminocarbonylethylenyl)-2(thio)-pseudouracil; 1 (aminocarbonylethylenyl)-2,4-(dithio)pseudouracil; 1 (aminocarbonylethylenyl)-4 (thio)pseudouracil; 1 (aminocarbonylethylenyl)-pseudouracil; 1 substituted 2(thio)-pseudouracil; 1 substituted 2,4-(dithio)pseudouracil; 1 substituted 4 (thio)pseudouracil; 1 substituted pseudouracil; 1-(aminoalkylamino-carbonylethylenyl)-2-(thio)-pseudouracil; 1-Methyl-3-(3-amino-3-carboxypropyl) pseudouridine TP; 1-Methyl-3-(3-amino-3-carboxypropyl) pseudo-UTP; 1-Methyl-pseudo-UTP; 2 (thio)pseudouracil; 2' deoxy uridine; 2' fluorouridine; 2-(thio)uracil; 2,4-(dithio) psuedouracil; 2' methyl, 2'amino, 2'azido, 2'fluro-guanosine; 2'-Amino-2'-deoxy-UTP; 2'-Azido-2'-deoxy-UTP; 2'-Azido-deoxyuridine TP; 2'-O-methylpseudouridine; 2' deoxy uridine; 2' fluorouridine; 2'-Deoxy-2'-a-aminouridine TP; 2'-Deoxy-2'-a-azidouridine TP; 2-methylpseudouridine; 3 (3 amino-3 carboxypropyl)uracil; 4 (thio)pseudouracil; 4-(thio)pseudouracil; 4-(thio)uracil; 4-thiouracil; 5 (1,3-diazole-1-alkyl)uracil; 5 (2-aminopropyl)uracil; 5 (aminoalkyl)uracil; 5 (dimethylaminoalkyl)uracil; 5 (guanidiniumalkyl)uracil; 5 (methoxycarbonylmethyl)-2-(thio)uracil; 5 (methoxycarbonyl-methyl)uracil; 5 (methyl) 2 (thio)uracil; 5 (methyl) 2,4 (dithio)uracil; 5 (methyl) 4 (thio)uracil; 5 (methylaminomethyl)-2 (thio)uracil; 5 (methylaminomethyl)-2,4 (dithio)uracil; 5 (methylaminomethyl)-4 (thio) uracil; 5 (propynyl)uracil; 5 (trifluoromethyl)uracil; 5-(2-aminopropyl)uracil; 5-(alkyl)-2-(thio)pseudouracil; 5-(alkyl)-2,4 (dithio)pseudouracil; 5-(alkyl)-4 (thio) pseudouracil; 5-(alkyl)pseudouracil; 5-(alkyl)uracil; 5-(alkynyl)uracil; 5-(allylamino)uracil; 5-(cyanoalkyl)uracil; 5-(dialkylaminoalkyl)uracil; 5-(dimethylaminoalkyl) uracil; 5-(guanidiniumalkyl)uracil; 5-(halo)uracil; 5-(1,3-diazole-1-alkyl)uracil; 5-(methoxy)uracil; 5-(methoxycarbonylmethyl)-2-(thio)uracil; 5-(methoxycarbonyl-methyl)uracil; 5-(methyl) 2(thio)uracil; 5-(methyl) 2,4 (dithio)uracil; 5-(methyl) 4 (thio)uracil; 5-(methyl)-2-(thio)pseudouracil; 5-(methyl)-2,4 (dithio)pseudouracil; 5-(methyl)-4 (thio)pseudouracil; 5-(methyl)pseudouracil; 5-(methylaminomethyl)-2 (thio)uracil; 5-(methylaminomethyl)-2,4(dithio)uracil; 5-(methylaminomethyl)-4-(thio) uracil; 5-(propynyl)uracil; 5-(trifluoromethyl)uracil; 5-aminoallyl-uridine; 5-bromo-uridine; 5-iodo-uridine; 5-uracil; 6 (azo)uracil; 6-(azo)uracil; 6-aza-uridine; allyamino-uracil; aza uracil; deaza uracil; N3 (methyl)uracil; Pseudo-UTP-1-2-ethanoic acid; Pseudouracil; 4-Thio-pseudo-UTP; 1-carboxymethyl-pseudouridine; 1-methyl-1-deaza-pseudouridine; 1-propynyl-uridine; 1-taurinomethyl-1-methyl-uridine; 1-taurinomethyl-4-thio-uridine; 1-taurinomethyl-pseudouridine; 2-methoxy-4-thio-pseudouridine; 2-thio-1-methyl-1-deaza-pseudouridine; 2-thio-1-methyl-

pseudouridine; 2-thio-5-aza-uridine; 2-thio-dihydropseudouridine; 2-thio-dihydrouridine; 2-thio-pseudouridine; 4-methoxy-2-thio-pseudouridine; 4-methoxy-pseudouridine; 4-thio-1-methyl-pseudouridine; 4-thio-pseudouridine; 5-aza-uridine; Dihydropseudouridine; (±)1-(2-Hydroxypropyl)pseudouridine TP; (2R)-1-(2-Hydroxypropyl)pseudouridine TP; (2S)-1-(2-Hydroxypropyl) pseudouridine TP; (E)-5-(2-Bromo-vinyl)ara-uridine TP; (E)-5-(2-Bromo-vinyl)uridine TP; (Z)-5-(2-Bromo-vinyl) ara-uridine TP; (Z)-5-(2-Bromo-vinyl)uridine TP; 1-(2,2,2-Trifluoroethyl)-pseudo-UTP; 1-(2,2,3,3,3-Pentafluoropropyl)pseudouridine TP; 1-(2,2-Diethoxyethyl)pseudouridine TP; 1-(2,4,6-Trimethylbenzyl)pseudouridine TP; 1-(2,4,6-Trimethyl-benzyl)pseudo-UTP; 1-(2,4,6-Trimethyl-phenyl) pseudo-UTP; 1-(2-Amino-2-carboxyethyl)pseudo-UTP; 1-(2-Amino-ethyl)pseudo-UTP; 1-(2-Hydroxyethyl) pseudouridine TP; 1-(2-Methoxyethyl)pseudouridine TP; 1-(3,4-Bis-trifluoromethoxybenzyl)pseudouridine TP; 1-(3,4-Dimethoxybenzyl)pseudouridine TP; 1-(3-Amino-3-carboxypropyl)pseudo-UTP; 1-(3-Amino-propyl)pseudo-UTP; 1-(3-Cyclopropyl-prop-2-ynyl)pseudouridine TP; 1-(4-Amino-4-carboxybutyl)pseudo-UTP; 1-(4-Amino-benzyl) pseudo-UTP; 1-(4-Amino-butyl)pseudo-UTP; 1-(4-Amino-phenyl)pseudo-UTP; 1-(4-Azidobenzyl)pseudouridine TP; 1-(4-Bromobenzyl)pseudouridine TP; 1-(4-Chlorobenzyl) pseudouridine TP; 1-(4-Fluorobenzyl)pseudouridine TP; 1-(4-Iodobenzyl)pseudouridine TP; 1-(4-Methanesulfonyl-benzyl)pseudouridine TP; 1-(4-Methoxybenzyl)pseudouridine TP; 1-(4-Methoxy-benzyl)pseudo-UTP; 1-(4-Methoxy-phenyl)pseudo-UTP; 1-(4-Methylbenzyl)pseudouridine TP; 1-(4-Methyl-benzyl)pseudo-UTP; 1-(4-Nitrobenzyl) pseudouridine TP; 1-(4-Nitro-benzyl)pseudo-UTP; 1(4-Nitro-phenyl)pseudo-UTP; 1-(4-Thiomethoxybenzyl) pseudouridine TP; 1-(4-Trifluoromethoxybenzyl) pseudouridine TP; 1-(4-Trifluoromethylbenzyl) pseudouridine TP; 1-(5-Amino-pentyl)pseudo-UTP; 1-(6-Amino-hexyl)pseudo-UTP; 1,6-Dimethyl-pseudo-UTP; 1-[3-(2-{2-[2-(2-Aminoethoxy)-ethoxy]-ethoxy}-ethoxy)-propionyl]pseudouridine TP; 1-{3-[2-(2-Aminoethoxy)-ethoxy]-propionyl}pseudouridine TP; 1-Acetylpseudouridine TP; 1-Alkyl-6-(1-propynyl)-pseudo-UTP; 1-Alkyl-6-(2-propynyl)-pseudo-UTP; 1-Alkyl-6-allyl-pseudo-UTP; 1-Alkyl-6-ethynyl-pseudo-UTP; 1-Alkyl-6-homoallyl-pseudo-UTP; 1-Alkyl-6-vinyl-pseudo-UTP; 1-Allylp-seudouridine TP; 1-Aminomethyl-pseudo-UTP; 1-Benzoylpseudouridine TP; 1-Benzyloxymethylpseudouridine TP; 1-Benzyl-pseudo-UTP; 1-Biotinyl-PEG2-pseudouridine TP; 1-Biotinylpseudouridine TP; 1-Butyl-pseudo-UTP; 1-Cyanomethylpseudouridine TP; 1-Cyclobutylmethyl-pseudo-UTP; 1-Cyclobutyl-pseudo-UTP; 1-Cycloheptylmethyl-pseudo-UTP; 1-Cycloheptyl-pseudo-UTP; 1-Cyclohexylmethyl-pseudo-UTP; 1-Cyclohexyl-pseudo-UTP; 1-Cyclooctylmethyl-pseudo-UTP; 1-Cyclooctyl-pseudo-UTP; 1-Cyclopentylmethyl-pseudo-UTP; 1-Cyclopentyl-pseudo-UTP; 1-Cyclopropylmethyl-pseudo-UTP; 1-Cyclopropyl-pseudo-UTP; 1-Ethyl-pseudo-UTP; 1-Hexyl-pseudo-UTP; 1-Homoallylpseudouridine TP; 1-Hydroxymethylpseudouridine TP; 1-iso-propyl-pseudo-UTP; 1-Me-2-thio-pseudo-UTP; 1-Me-4-thio-pseudo-UTP; 1-Me-alpha-thio-pseudo-UTP; 1-Methanesulfonylmethylp-seudouridine TP; 1-Methoxymethylpseudouridine TP; 1-Methyl-6-(2,2,2-Trifluoroethyl)pseudo-UTP; 1-Methyl-6-(4-morpholino)-pseudo-UTP; 1-Methyl-6-(4-thiomorpholino)-pseudo-UTP; 1-Methyl-6-(substituted phenyl) pseudo-UTP; 1-Methyl-6-amino-pseudo-UTP; 1-Methyl-6-azido-pseudo-UTP; 1-Methyl-6-bromo-pseudo-UTP; 1-Methyl-6-butyl-pseudo-UTP; 1-Methyl-6-chloro-pseudo-UTP; 1-Methyl-6-cyano-pseudo-UTP; 1-Methyl-6-dimethylamino-pseudo-UTP; 1-Methyl-6-ethoxy-pseudo-UTP; 1-Methyl-6-ethylcarboxylate-pseudo-UTP; 1-Methyl-6-ethyl-pseudo-UTP; 1-Methyl-6-fluoro-pseudo-UTP; 1-Methyl-6-formyl-pseudo-UTP; 1-Methyl-6-hydroxyamino-pseudo-UTP; 1-Methyl-6-hydroxy-pseudo-UTP; 1-Methyl-6-iodo-pseudo-UTP; 1-Methyl-6-iso-propyl-pseudo-UTP; 1-Methyl-6-methoxy-pseudo-UTP; 1-Methyl-6-methylamino-pseudo-UTP; 1-Methyl-6-phenyl-pseudo-UTP; 1-Methyl-6-propyl-pseudo-UTP; 1-Methyl-6-tert-butyl-pseudo-UTP; 1-Methyl-6-trifluoromethoxy-pseudo-UTP; 1-Methyl-6-trifluoromethyl-pseudo-UTP; 1-Morpholinomethylpseudouridine TP; 1-Pentyl-pseudo-UTP; 1-Phenyl-pseudo-UTP; 1-Pivaloylpseudouridine TP; 1-Propargylpseudouridine TP; 1-Propyl-pseudo-UTP; 1-propynyl-pseudouridine; 1-p-tolyl-pseudo-UTP; 1-tert-Butyl-pseudo-UTP; 1-Thiomethoxymethylpseudouridine TP; 1-Thiomorpholinomethylpseudouridine TP; 1-Trifluoroacetylpseudouridine TP; 1-Trifluoromethyl-pseudo-UTP; 1-Vinylpseudouridine TP; 2,2'-anhydro-uridine TP; 2'-bromo-deoxyuridine TP; 2'-F-5-Methyl-2'-deoxy-UTP; 2'-OMe-5-Me-UTP; 2'-OMe-pseudo-UTP; 2'-a-Ethynyluridine TP; 2'-a-Trifluoromethyluridine TP; 2'-b-Ethynyluridine TP; 2'-b-Trifluoromethyluridine TP; 2'-Deoxy-2',2'-difluorouridine TP; 2'-Deoxy-2'-a-mercaptouridine TP; 2'-Deoxy-2'-a-thiomethoxyuridine TP; 2'-Deoxy-2'-b-aminouridine TP; 2'-Deoxy-2'-b-azidouridine TP; 2'-Deoxy-2'-b-bromouridine TP; 2'-Deoxy-2'-b-chlorouridine TP; 2'-Deoxy-2'-b-fluorouridine TP; 2'-Deoxy-2'-b-iodouridine TP; 2'-Deoxy-2'-b-mercaptouridine TP; 2'-Deoxy-2'-b-thiomethoxyuridine TP; 2-methoxy-4-thio-uridine; 2-methoxyuridine; 2'-O-Methyl-5-(1-propynyl)uridine TP; 3-Alkyl-pseudo-UTP; 4'-Azidouridine TP; 4'-Carbocyclic uridine TP; 4'-Ethynyluridine TP; 5-(1-Propynyl)ara-uridine TP; 5-(2-Furanyl)uridine TP; 5-Cyanouridine TP; 5-Dimethylaminouridine TP; 5'-Homo-uridine TP; 5-iodo-2'-fluoro-deoxyuridine TP; 5-Phenylethynyluridine TP; 5-Trideuteromethyl-6-deuterouridine TP; 5-Trifluoromethyl-Uridine TP; 5-Vinylarauridine TP; 6-(2,2,2-Trifluoroethyl)-pseudo-UTP; 6-(4-Morpholino)-pseudo-UTP; 6-(4-Thiomorpholino)-pseudo-UTP; 6-(Substituted-Phenyl)-pseudo-UTP; 6-Amino-pseudo-UTP; 6-Azido-pseudo-UTP; 6-Bromo-pseudo-UTP; 6-Butyl-pseudo-UTP; 6-Chloro-pseudo-UTP; 6-Cyano-pseudo-UTP; 6-Dimethylamino-pseudo-UTP; 6-Ethoxy-pseudo-UTP; 6-Ethylcarboxylate-pseudo-UTP; 6-Ethyl-pseudo-UTP; 6-Fluoro-pseudo-UTP; 6-Formyl-pseudo-UTP; 6-Hydroxyamino-pseudo-UTP; 6-Hydroxy-pseudo-UTP; 6-Iodo-pseudo-UTP; 6-iso-Propyl-pseudo-UTP; 6-Methoxy-pseudo-UTP; 6-Methylamino-pseudo-UTP; 6-Methyl-pseudo-UTP; 6-Phenyl-pseudo-UTP; 6-Phenyl-pseudo-UTP; 6-Propyl-pseudo-UTP; 6-tert-Butyl-pseudo-UTP; 6-Trifluoromethoxy-pseudo-UTP; 6-Trifluoromethyl-pseudo-UTP; Alpha-thio-pseudo-UTP; Pseudouridine 1-(4-methylbenzenesulfonic acid) TP; Pseudouridine 1-(4-methylbenzoic acid) TP; Pseudouridine TP 1-[3-(2-ethoxy)]propionic acid; Pseudouridine TP 1-[3-{2-(2-[2-(2-ethoxy)-ethoxy]-ethoxy)-ethoxy}]propionic acid; Pseudouridine TP 1-[3-{2-(2-[2-{2 (2-ethoxy)-ethoxy}-ethoxy]-ethoxy)-ethoxy}]propionic acid; Pseudouridine TP 1-[3-{2-(2-[2-ethoxy]-ethoxy)-ethoxy}]propionic acid; Pseudouridine TP 1-[3-{2-(2-ethoxy)-ethoxy}] propionic acid; Pseudouridine TP 1-methylphosphonic acid; Pseudouridine TP 1-methylphosphonic acid diethyl ester; Pseudo-UTP-N1-3-propionic acid; Pseudo-UTP-N1-4-butanoic acid; Pseudo-UTP-N1-5-pentanoic acid; Pseudo-UTP-N1-6-hexanoic acid; Pseudo-UTP-N1-7-heptanoic acid; Pseudo-UTP-N1-methyl-p-ben-

zoic acid; Pseudo-UTP-N1-p-benzoic acid; Wybutosine; Hydroxywybutosine; Isowyosine; Peroxywybutosine; undermodified hydroxywybutosine; 4-demethylwyosine; 2,6-(diamino)purine; 1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl: 1,3-(diaza)-2-(oxo)-phenthiazin-1-yl; 1,3-(diaza)-2-(oxo)-phenoxazin-1-yl; 1,3,5-(triaza)-2,6-(dioxa)-naphthalene; 2 (amino)purine; 2,4,5-(trimethyl)phenyl; 2' methyl, 2'amino, 2'azido, 2'fluro-cytidine; 2' methyl, 2'amino, 2'azido, 2'fluro-adenine; 2'methyl, 2'amino, 2'azido, 2'fluro-uridine; 2'-amino-2'-deoxyribose; 2-amino-6-Chloro-purine; 2-aza-inosinyl; 2'-azido-2'-deoxyribose; 2'fluoro-2'-deoxyribose; 2'-fluoro-modified bases; 2'-O-methyl-ribose; 2-oxo-7-aminopyridopyrimidin-3-yl; 2-oxo-pyridopyrimidine-3-yl; 2-pyridinone; 3 nitropyrrole; 3-(methyl)-7-(propynyl) isocarbostyrilyl; 3-(methyl)isocarbostyrilyl; 4-(fluoro)-6-(methyl)benzimidazole; 4-(methyl)benzimidazole; 4-(methyl)indolyl; 4,6-(dimethyl)indolyl; 5 nitroindole; 5 substituted pyrimidines; 5-(methyl)isocarbostyrilyl; 5-nitroindole; 6-(aza)pyrimidine; 6-(azo)thymine; 6-(methyl)-7-(aza)indolyl; 6-chloro-purine; 6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; 7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl; 7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl; 7-(aminoalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-1-yl; 7-(aminoalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenthiazin-1-yl;
7-(aminoalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-1-yl; 7-(aza)indolyl; 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazinl-yl; 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl;
7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl; 7-(guanidiniumalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-1-yl; 7-(guanidiniumalkyl-hydroxy)-1,3-(diaza)-2-(oxo)-phenthiazin-1-yl;
7-(guanidiniumalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-1-yl; 7-(propynyl)isocarbostyrilyl; 7-(propynyl)isocarbostyrilyl, propynyl-7-(aza)indolyl; 7-deaza-inosinyl; 7-substituted 1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl; 7-substituted 1,3-(diaza)-2-(oxo)-phenoxazin-1-yl; 9-(methyl)-imidizopyridinyl; Aminoindolyl; Anthracenyl; bis-ortho-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; bis-ortho-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; Difluorotolyl; Hypoxanthine; Imidizopyridinyl; Inosinyl; Isocarbostyrilyl; Isoguanisine; N2-substituted purines; N6-methyl-2-amino-purine; N6-substituted purines; N-alkylated derivative; Napthalenyl; Nitrobenzimidazolyl; Nitroimidazolyl; Nitroindazolyl; Nitropyrazolyl; Nubularine; 06-substituted purines; O-alkylated derivative; ortho-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; ortho-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; Oxoformycin TP; para-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; para-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; Pentacenyl; Phenanthracenyl; Phenyl; propynyl-7-(aza)indolyl; Pyrenyl; pyridopyrimidin-3-yl; pyridopyrimidin-3-yl, 2-oxo-7-amino-pyridopyrimidin-3-yl; pyrrolo-pyrimidin-2-on-3-yl; Pyrrolopyrimidinyl; Pyrrolopyrizinyl; Stilbenzyl; substituted 1,2,4-triazoles; Tetracenyl; Tubercidine; Xanthine; Xanthosine-5'-TP; 2-thio-zebularine; 5-aza-2-thio-zebularine; 7-deaza-2-amino-purine; pyridin-4-one ribonucleoside; 2-Amino-riboside-TP; Formycin A TP; Formycin B TP; Pyrrolosine TP; 2'-OH-ara-adenosine TP; 2'-OH-ara-cytidine TP; 2'-OH-ara-uridine TP; 2'-OH-ara-guanosine TP; 5-(2-carbomethoxyvinyl)uridine TP; and N6-(19-Amino-pentaoxanonadecyl)adenosine TP.

In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) include a combination of at least two (e.g., 2, 3, 4 or more) of the aforementioned modified nucleobases.

In some embodiments, modified nucleobases in polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) are selected from the group consisting of pseudouridine (ψ), N1-methylpseudouridine ($m^1\psi$), N1-ethylpseudouridine, 2-thiouridine, 4'-thiouridine, 5-methylcytosine, 2-thio-1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-pseudouridine, 2-thio-5-aza-uridine, 2-thio-dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-pseudouridine, 4-methoxy-2-thio-pseudouridine, 4-methoxy-pseudouridine, 4-thio-1-methyl-pseudouridine, 4-thio-pseudouridine, 5-aza-uridine, dihydropseudouridine, 5-methoxyuridine and 2'-O-methyl uridine. In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) include a combination of at least two (e.g., 2, 3, 4 or more) of the aforementioned modified nucleobases.

In some embodiments, modified nucleobases in polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) are selected from the group consisting of 1-methyl-pseudouridine ($m^1\psi$), 5-methoxy-uridine (mo^5U), 5-methyl-cytidine (m^5C), pseudouridine (ψ), α-thio-guanosine and α-thio-adenosine. In some embodiments, polynucleotides includes a combination of at least two (e.g., 2, 3, 4 or more) of the aforementioned modified nucleobases.

In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise pseudouridine (ψ) and 5-methyl-cytidine (m^5C). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise 1-methyl-pseudouridine ($m^1\psi$). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise 1-methyl-pseudouridine ($m^1\psi$) and 5-methyl-cytidine (m^5C). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise 2-thiouridine (s^2U). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise 2-thiouridine and 5-methyl-cytidine (m^5C). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise methoxy-uridine (mo^5U). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise 5-methoxy-uridine (mo^5U) and 5-methyl-cytidine (m^5C). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise 2'-O-methyl uridine. In some embodiments polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise 2'-O-methyl uridine and 5-methyl-cytidine (m^5C). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise N6-methyl-adenosine (m^6A). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise N6-methyl-adenosine (m^6A) and 5-methyl-cytidine (m^5C).

In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) are uniformly modified (e.g., fully modified, modified throughout the entire sequence) for a particular modification. For example, a polynucleotide can be uniformly modified with 5-methyl-cytidine (m^5C), meaning that all cytosine residues in the mRNA sequence are replaced with 5-methyl-cytidine (m^5C). Similarly, a polynucleotide can be uniformly modified for any type of nucleoside residue present in the sequence by replacement with a modified residue such as those set forth above.

Exemplary nucleobases and nucleosides having a modified cytosine include N4-acetyl-cytidine (ac4C), 5-methyl-cytidine (m5C), 5-halo-cytidine (e.g., 5-iodo-cytidine), 5-hydroxymethyl-cytidine (hm5C), 1-methyl-pseudoisocytidine, 2-thio-cytidine (s2C), and 2-thio-5-methyl-cytidine.

In some embodiments, a modified nucleobase is a modified uridine. Exemplary nucleobases and In some embodiments, a modified nucleobase is a modified cytosine. nucleosides having a modified uridine include 5-cyano uridine, and 4'-thio uridine.

In some embodiments, a modified nucleobase is a modified adenine. Exemplary nucleobases and nucleosides having a modified adenine include 7-deaza-adenine, 1-methyl-adenosine (m1A), 2-methyl-adenine (m2A), and N6-methyl-adenosine (m6A).

In some embodiments, a modified nucleobase is a modified guanine. Exemplary nucleobases and nucleosides having a modified guanine include inosine (I), 1-methyl-inosine (m1I), wyosine (imG), methylwyosine (mimG), 7-deaza-guanosine, 7-cyano-7-deaza-guanosine (preQ0), 7-aminomethyl-7-deaza-guanosine (preQ1), 7-methyl-guanosine (m7G), 1-methyl-guanosine (m1G), 8-oxo-guanosine, 7-methyl-8-oxo-guanosine.

The polynucleotides of the present disclosure may be partially or fully modified along the entire length of the molecule. For example, one or more or all or a given type of nucleotide (e.g., purine or pyrimidine, or any one or more or all of A, G, U, C) may be uniformly modified in a polynucleotide of the disclosure, or in a given predetermined sequence region thereof (e.g., in the mRNA including or excluding the polyA tail). In some embodiments, all nucleotides X in a polynucleotide of the present disclosure (or in a given sequence region thereof) are modified nucleotides, wherein X may any one of nucleotides A, G, U, C, or any one of the combinations A+G, A+U, A+C, G+U, G+C, U+C, A+G+U, A+G+C, G+U+C or A+G+C.

The polynucleotide may contain from about 1% to about 100% modified nucleotides (either in relation to overall nucleotide content, or in relation to one or more types of nucleotide, i.e., any one or more of A, G, U or C) or any intervening percentage (e.g., from 1% to 20%, from 1% to 25%, from 1% to 50%, from 1% to 60%, from 1% to 70%, from 1% to 80%, from 1% to 90%, from 1% to 95%, from 10% to 20%, from 10% to 25%, from 10% to 50%, from 10% to 60%, from 10% to 70%, from 10% to 80%, from 10% to 90%, from 10% to 95%, from 10% to 100%, from 20% to 25%, from 20% to 50%, from 20% to 60%, from 20% to 70%, from 20% to 80%, from 20% to 90%, from 20% to 95%, from 20% to 100%, from 50% to 60%, from 50% to 70%, from 50% to 80%, from 50% to 90%, from 50% to 95%, from 50% to 100%, from 70% to 80%, from 70% to 90%, from 70% to 95%, from 70% to 100%, from 80% to 90%, from 80% to 95%, from 80% to 100%, from 90% to 95%, from 90% to 100%, and from 95% to 100%). Any remaining percentage is accounted for by the presence of unmodified A, G, U, or C.

The polynucleotides may contain at a minimum 1% and at maximum 100% modified nucleotides, or any intervening percentage, such as at least 5% modified nucleotides, at least 10% modified nucleotides, at least 25% modified nucleotides, at least 50% modified nucleotides, at least 80% modified nucleotides, or at least 90% modified nucleotides. For example, the polynucleotides may contain a modified pyrimidine such as a modified uracil or cytosine. In some embodiments, at least 5%, at least 10%, at least 25%, at least 50%, at least 80%, at least 90% or 100% of the uracil in the polynucleotide is replaced with a modified uracil (e.g., a 5-substituted uracil). The modified uracil can be replaced by a compound having a single unique structure, or can be replaced by a plurality of compounds having different structures (e.g., 2, 3, 4 or more unique structures). n some embodiments, at least 5%, at least 10%, at least 25%, at least 50%, at least 80%, at least 90% or 100% of the cytosine in the polynucleotide is replaced with a modified cytosine (e.g., a 5-substituted cytosine). The modified cytosine can be replaced by a compound having a single unique structure, or can be replaced by a plurality of compounds having different structures (e.g., 2, 3, 4 or more unique structures).

Thus, in some embodiments, the RNA (e.g., mRNA) vaccines comprise a 5'UTR element, an optionally codon optimized open reading frame, and a 3'UTR element, a poly(A) sequence and/or a polyadenylation signal wherein the RNA is not chemically modified.

In some embodiments, the modified nucleobase is a modified uracil. Exemplary nucleobases and nucleosides having a modified uracil include pseudouridine (ψ), pyridin-4-one ribonucleoside, 5-aza-uridine, 6-aza-uridine, 2-thio-5-aza-uridine, 2-thio-uridine (s^2U), 4-thio-uridine (s^4U), 4-thio-pseudouridine, 2-thio-pseudouridine, 5-hydroxy-uridine (ho^5U), 5-aminoallyl-uridine, 5-halo-uridine (e.g., 5-iodo-uridineor 5-bromo-uridine), 3-methyl-uridine (m^3U), 5-methoxy-uridine (mo^5U), uridine 5-oxyacetic acid (cmo^5U), uridine 5-oxyacetic acid methyl ester ($mcmo^5U$), 5-carboxymethyl-uridine (cm^5U), 1-carboxymethyl-pseudouridine, 5-carboxyhydroxymethyl-uridine (chm^5U), 5-carboxyhydroxymethyl-uridine methyl ester ($mchm^5U$), 5-methoxycarbonylmethyl-uridine (mcm^5U), 5-methoxycarbonylmethyl-2-thio-uridine (mcm^5s^2U), 5-aminomethyl-2-thio-uridine (nm^5s^2U), 5-methylaminomethyl-uridine (mnm^5U), 5-methylaminomethyl-2-thio-uridine (mnm^5s^2U), 5-methylaminomethyl-2-seleno-uridine (mnm^5se^2U), 5-carbamoylmethyl-uridine (ncm^5U), 5-carboxymethylaminomethyl-uridine ($cmnm^5U$), 5-carboxymethylaminomethyl-2-thio-uridine ($cmnm^5s^2U$), 5-propynyl-uridine, 1-propynyl-pseudouridine, 5-taurinomethyl-uridine (τm^5U), 1-taurinomethyl-pseudouridine, 5-taurinomethyl-2-thio-uridine (τm^5s^2U), 1-taurinomethyl-4-thio-pseudouridine, 5-methyl-uridine (m^5U, i.e., having the nucleobase deoxythymine), 1-methyl-pseudouridine ($m^1\psi$), 5-methyl-2-thio-uridine (m^5s^2U), 1-methyl-4-thio-pseudouridine ($m^1s^4\psi$), 4-thio-1-methyl-pseudouridine, 3-methyl-pseudouridine ($m^3\psi$), 2-thio-1-methyl-pseudouridine, 1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-1-deaza-pseudouridine, dihydrouridine (D), dihydropseudouridine, 5,6-dihydrouridine, 5-methyldihydrouridine (m^5D), 2-thio-dihydrouridine, 2-thio-dihydropseudouridine, 2-methoxy-uridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, 4-methoxy-2-thio-pseudouridine, N1-methyl-pseudouridine, 3-(3-amino-3-carboxypropyl)uridine (acp^3U), 1-methyl-3-(3-amino-3-carboxypropyl)pseudouridine ($acp^3\psi$), 5-(isopentenylaminomethyl)uridine (inm^5U), 5-(isopentenylaminomethyl)-2-thio-uridine (inm^5s^2U), α-thio-uridine, 2'-O-methyl-uridine (Urn), 5,2'-O-dimethyl-uridine (m^5Um), 2'-O-methyl-pseudouridine (ψm), 2-thio-2'-O-methyl-uridine (s^2Um), 5-methoxycarbonylmethyl-2'-O-methyl-uridine (mcm^5Um), 5-carbamoylmethyl-2'-O-methyl-uridine (ncm^5Um), 5-carboxymethylaminomethyl-2'-O-methyl-uridine ($cmnm^5Um$), 3,2'-O-dimethyl-uridine (m^3Um), and 5-(isopentenylaminomethyl)-2'-O-methyl-uridine (inm^5Um), 1-thio-uridine, deoxythymidine, 2'-F-ara-uridine, 2'-F-uridine, 2'-0H-ara-uridine, 5-(2-carbomethoxyvinyl) uridine, and 5-[3-(1-E-propenylamino)] uridine.

In some embodiments, the modified nucleobase is a modified cytosine. Exemplary nucleobases and nucleosides having a modified cytosine include 5-aza-cytidine, 6-aza-cytidine, pseudoisocytidine, 3-methyl-cytidine (m^3C), N4-acetyl-cytidine (ac^4C), 5-formylcytidine (f^5C), N4-methyl-cytidine (m^4C), 5-methyl-cytidine (m^5C), 5-halo-cytidine (e.g., 5-iodo-cytidine), 5-hydroxymethyl-cytidine (hm^5C), 1-methyl-pseudoisocytidine, pyrrolo-cytidine, pyrrolo-pseudoisocytidine, 2-thio-cytidine (s^2C), 2-thio-5-methyl-cytidine, 4-thio-pseudoisocytidine, 4-thio-1-methyl-pseudoisocytidine, 4-thio-1-methyl-1-deaza-pseudoisocytidine, 1-methyl-1-deaza-pseudoisocytidine, zebularine, 5-aza-zebularine, 5-methyl-zebularine, 5-aza-2-thio-zebularine, 2-thio-zebularine, 2-methoxy-cytidine, 2-methoxy-5-methyl-cytidine, 4-methoxy-pseudoisocytidine, 4-methoxy-1-methyl-pseudoisocytidine, lysidine (k_2C), α-thio-cytidine, 2'-O-methyl-cytidine (Cm), 5,2'-O-dimethylcytidine (m^5Cm), N4-acetyl-2'-O-methyl-cytidine (ac^4Cm), N4,2'-O-dimethylcytidine (m^4Cm), 5-formyl-2'-O-methyl-cytidine (f^5Cm), N4,N4,2'-O-trimethyl-cytidine ($m^4{}_2Cm$), 1-thio-cytidine, 2'-F-ara-cytidine, 2'-F-cytidine, and 2'-0H-ara-cytidine.

In some embodiments, the modified nucleobase is a modified adenine. Exemplary nucleobases and nucleosides having a modified adenine include 2-amino-purine, 2,6-diaminopurine, 2-amino-6-halo-purine (e.g., 2-amino-6-chloro-purine), 6-halo-purine (e.g., 6-chloro-purine), 2-amino-6-methyl-purine, 8-azido-adenosine, 7-deaza-adenine, 7-deaza-8-aza-adenine, 7-deaza-2-amino-purine, 7-deaza-8-aza-2-amino-purine, 7-deaza-2,6-diaminopurine, 7-deaza-8-aza-2,6-diaminopurine, 1-methyl-adenosine (m^1A), 2-methyl-adenine (m^2A), N6-methyl-adenosine (m^6A), 2-methylthio-N6-methyl-adenosine ($ms^2\ m^6A$), N6-isopentenyl-adenosine (i^6A), 2-methylthio-N6-isopentenyl-adenosine (ms^2i^6A), N6-(cis-hydroxyisopentenyl)adenosine (io^6A), 2-methylthio-N6-(cis-hydroxyisopentenyl) adenosine (ms^2io^6A), N6-glycinylcarbamoyl-adenosine (g^6A), N6-threonylcarbamoyl-adenosine (t^6A), N6-methyl-N6-threonylcarbamoyl-adenosine (m^6t^6A), 2-methylthio-N6-threonylcarbamoyl-adenosine (ms^2g^6A), N6,N6-dimethyl-adenosine ($m^6{}_2A$), N6-hydroxynorvalylcarbamoyl-adenosine (hn^6A), 2-methylthio-N6-hydroxynorvalylcarbamoyl-adenosine (ms^2hn^6A), N6-acetyl-adenosine (ac^6A), 7-methyl-adenine, 2-methylthio-adenine, 2-methoxy-adenine, α-thio-adenosine, 2'-O-methyl-adenosine (Am), N6,2'-O-dimethyl-adenosine (m^6Am), N6,N6,2'-O-trimethyl-adenosine ($m^6{}_2Am$), 1,2'-O-dimethyl-adenosine (m^1Am), 2'-O-ribosyladenosine (phosphate) (Ar(p)), 2-amino-N6-methyl-purine, 1-thio-adenosine, 8-azido-adenosine, 2'-F-ara-adenosine, 2'-F-adenosine, 2'-0H-ara-adenosine, and N6-(19-amino-pentaoxanonadecyl)-adenosine.

In some embodiments, the modified nucleobase is a modified guanine. Exemplary nucleobases and nucleosides having a modified guanine include inosine (I), 1-methyl-inosine (m^1I), wyosine (imG), methylwyosine (mimG), 4-demethyl-wyosine (imG-14), isowyosine (imG2), wybutosine (yW), peroxywybutosine (o_2yW), hydroxywybutosine (OhyW), undermodified hydroxywybutosine (OhyW*), 7-deaza-guanosine, queuosine (Q), epoxyqueuosine (oQ), galactosyl-queuosine (galQ), mannosyl-queuosine (manQ), 7-cyano-7-deaza-guanosine ($preQ_0$), 7-aminomethyl-7-deaza-guanosine ($preQ_1$), archaeosine (G±), 7-deaza-8-aza-guanosine, 6-thio-guanosine, 6-thio-7-deaza-guanosine, 6-thio-7-deaza-8-aza-guanosine, 7-methyl-guanosine (m^7G), 6-thio-7-methyl-guanosine, 7-methyl-inosine, 6-methoxy-guanosine, 1-methyl-guanosine (m^1G), N2-methyl-guanosine (m^2G), N2,N2-dimethyl-guanosine ($m^2{}_2G$), N2,7-dimethyl-guano sine ($m^{2,7}G$), N2,N2,7-dimethyl-guanosine ($m^{2,2,7}G$), 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, 1-methyl-6-thio-guanosine, N2-methyl-6-thio-guanosine, N2,N2-dimethyl-6-thio-guanosine, α-thio-guanosine, 2'-O-methyl-guanosine (Gm), N2-methyl-2'-O-methyl-guanosine (m^2Gm), N2,N2-dimethyl-2'-O-methyl-guanosine ($m^2{}_2Gm$), 1-methyl-2'-O-methyl-guanosine (m^1Gm), N2,7-dimethyl-2'-O-methyl-guanosine ($m^{2,7}Gm$), 2'-O-methyl-inosine (Im), 1,2'-O-dimethyl-inosine (m^1Im), 2'-O-ribosylguanosine (phosphate) (Gr(p)), 1-thio-guanosine, 06-methyl-guanosine, 2'-F-ara-guanosine, and 2'-F-guanosine.

N-Linked Glycosylation Site Mutants

N-linked glycans of viral proteins play important roles in modulating the immune response. Glycans can be important for maintaining the appropriate antigenic conformations, shielding potential neutralization epitopes, and may alter the proteolytic susceptibility of proteins. Some viruses have putative N-linked glycosylation sites. Deletion or modification of an N-linked glycosylation site may enhance the immune response. Thus, the present disclosure provides, in some embodiments, RNA (e.g., mRNA) vaccines comprising nucleic acids (e.g., mRNA) encoding antigenic polypeptides that comprise a deletion or modification at one or more N-linked glycosylation sites.

In Vitro Transcription of RNA (e.g., mRNA)

Respiratory virus vaccines of the present disclosure comprise at least one RNA polynucleotide, such as a mRNA (e.g., modified mRNA). mRNA, for example, is transcribed in vitro from template DNA, referred to as an "in vitro transcription template." In some embodiments, an in vitro transcription template encodes a 5' untranslated (UTR) region, contains an open reading frame, and encodes a 3' UTR and a polyA tail. The particular nucleic acid sequence composition and length of an in vitro transcription template will depend on the mRNA encoded by the template.

A "5' untranslated region" (5'UTR) refers to a region of an mRNA that is directly upstream (i.e., 5') from the start codon (i.e., the first codon of an mRNA transcript translated by a ribosome) that does not encode a polypeptide.

A "3' untranslated region" (3'UTR) refers to a region of an mRNA that is directly downstream (i.e., 3') from the stop codon (i.e., the codon of an mRNA transcript that signals a termination of translation) that does not encode a polypeptide.

An "open reading frame" is a continuous stretch of DNA beginning with a start codon (e.g., methionine (ATG)), and ending with a stop codon (e.g., TAA, TAG or TGA) and encodes a polypeptide.

A "polyA tail" is a region of mRNA that is downstream, e.g., directly downstream (i.e., 3'), from the 3' UTR that contains multiple, consecutive adenosine monophosphates. A polyA tail may contain 10 to 300 adenosine monophosphates. For example, a polyA tail may contain 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290 or 300 adenosine monophosphates. In some embodiments, a polyA tail contains 50 to 250 adenosine monophosphates. In a relevant biological setting (e.g., in cells, in vivo) the poly(A) tail functions to protect mRNA from enzymatic degradation, e.g., in the cytoplasm, and aids in transcription termination, export of the mRNA from the nucleus and translation.

In some embodiments, a polynucleotide includes 200 to 3,000 nucleotides. For example, a polynucleotide may include 200 to 500, 200 to 1000, 200 to 1500, 200 to 3000,

500 to 1000, 500 to 1500, 500 to 2000, 500 to 3000, 1000 to 1500, 1000 to 2000, 1000 to 3000, 1500 to 3000, or 2000 to 3000 nucleotides.

Flagellin Adjuvants

Flagellin is an approximately 500 amino acid monomeric protein that polymerizes to form the flagella associated with bacterial motion. Flagellin is expressed by a variety of flagellated bacteria (*Salmonella typhimurium* for example) as well as non-flagellated bacteria (such as *Escherichia coli*). Sensing of flagellin by cells of the innate immune system (dendritic cells, macrophages, etc.) is mediated by the Toll-like receptor 5 (TLR5) as well as by Nod-like receptors (NLRs) Ipaf and Naip5. TLRs and NLRs have been identified as playing a role in the activation of innate immune response and adaptive immune response. As such, flagellin provides an adjuvant effect in a vaccine.

The nucleotide and amino acid sequences encoding known flagellin polypeptides are publicly available in the NCBI GenBank database. The flagellin sequences from *S. Typhimurium, H. Pylori, V. Cholera, S. marcesens, S. flexneri, T. Pallidum, L. pneumophila, B. burgdorferei, C. difficile, R. meliloti, A. tumefaciens, R. lupini, B. clarridgeiae, P. Mirabilis, B. subtilus, L. monocytogenes, P. aeruginosa*, and *E. coli*, among others are known.

A flagellin polypeptide, as used herein, refers to a full length flagellin protein, immunogenic fragments thereof, and peptides having at least 50% sequence identify to a flagellin protein or immunogenic fragments thereof. Exemplary flagellin proteins include flagellin from *Salmonella typhi* (UniPro Entry number: Q56086), *Salmonella typhimurium* (A0A0C9DG09), *Salmonella enteritidis* (A0A0C9BAB7), and *Salmonella choleraesuis* (Q6V2X8), and SEQ ID NO: 54-56 (Table 17). In some embodiments, the flagellin polypeptide has at least 60%, 70%, 75%, 80%, 90%, 95%, 97%, 98%, or 99% sequence identify to a flagellin protein or immunogenic fragments thereof.

In some embodiments, the flagellin polypeptide is an immunogenic fragment. An immunogenic fragment is a portion of a flagellin protein that provokes an immune response. In some embodiments, the immune response is a TLR5 immune response. An example of an immunogenic fragment is a flagellin protein in which all or a portion of a hinge region has been deleted or replaced with other amino acids. For example, an antigenic polypeptide may be inserted in the hinge region. Hinge regions are the hypervariable regions of a flagellin. Hinge regions of a flagellin are also referred to as "D3 domain or region, "propeller domain or region," "hypervariable domain or region" and "variable domain or region." "At least a portion of a hinge region," as used herein, refers to any part of the hinge region of the flagellin, or the entirety of the hinge region. In other embodiments an immunogenic fragment of flagellin is a 20, 25, 30, 35, or 40 amino acid C-terminal fragment of flagellin.

The flagellin monomer is formed by domains D0 through D3. D0 and D1, which form the stem, are composed of tandem long alpha helices and are highly conserved among different bacteria. The D1 domain includes several stretches of amino acids that are useful for TLR5 activation. The entire D1 domain or one or more of the active regions within the domain are immunogenic fragments of flagellin. Examples of immunogenic regions within the D1 domain include residues 88-114 and residues 411-431 (in *Salmonella typhimurium* FliC flagellin. Within the 13 amino acids in the 88-100 region, at least 6 substitutions are permitted between *Salmonella* flagellin and other flagellins that still preserve TLR5 activation. Thus, immunogenic fragments of flagellin include flagellin like sequences that activate TLR5 and contain a 13 amino acid motif that is 53% or more identical to the *Salmonella* sequence in 88-100 of FliC (LQRVRELAVQSAN; SEQ ID NO: 84).

In some embodiments, the RNA (e.g., mRNA) vaccine includes an RNA that encodes a fusion protein of flagellin and one or more antigenic polypeptides. A "fusion protein" as used herein, refers to a linking of two components of the construct. In some embodiments, a carboxy-terminus of the antigenic polypeptide is fused or linked to an amino terminus of the flagellin polypeptide. In other embodiments, an amino-terminus of the antigenic polypeptide is fused or linked to a carboxy-terminus of the flagellin polypeptide. The fusion protein may include, for example, one, two, three, four, five, six or more flagellin polypeptides linked to one, two, three, four, five, six or more antigenic polypeptides. When two or more flagellin polypeptides and/or two or more antigenic polypeptides are linked such a construct may be referred to as a "multimer."

Each of the components of a fusion protein may be directly linked to one another or they may be connected through a linker. For instance, the linker may be an amino acid linker. The amino acid linker encoded for by the RNA (e.g., mRNA) vaccine to link the components of the fusion protein may include, for instance, at least one member selected from the group consisting of a lysine residue, a glutamic acid residue, a serine residue and an arginine residue. In some embodiments the linker is 1-30, 1-25, 1-25, 5-10, 5, 15, or 5-20 amino acids in length.

In other embodiments the RNA (e.g., mRNA) vaccine includes at least two separate RNA polynucleotides, one encoding one or more antigenic polypeptides and the other encoding the flagellin polypeptide. The at least two RNA polynucleotides may be co-formulated in a carrier such as a lipid nanoparticle.

Broad Spectrum RNA (e.g., mRNA) Vaccines

There may be situations where persons are at risk for infection with more than one strain of hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1). RNA (e.g., mRNA) therapeutic vaccines are particularly amenable to combination vaccination approaches due to a number of factors including, but not limited to, speed of manufacture, ability to rapidly tailor vaccines to accommodate perceived geographical threat, and the like. Moreover, because the vaccines utilize the human body to produce the antigenic protein, the vaccines are amenable to the production of larger, more complex antigenic proteins, allowing for proper folding, surface expression, antigen presentation, etc. in the human subject. To protect against more than one strain of hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1), a combination vaccine can be administered that includes RNA (e.g., mRNA) encoding at least one antigenic polypeptide protein (or antigenic portion thereof) of a first respiratory virus and further includes RNA encoding at least one antigenic polypeptide protein (or antigenic portion thereof) of a second respiratory virus. RNA (e.g., mRNA) can be co-formulated, for example, in a single lipid nanoparticle (LNP) or can be formulated in separate LNPs for co-administration.

Methods of Treatment

Provided herein are compositions (e.g., pharmaceutical compositions), methods, kits and reagents for prevention and/or treatment of respiratory diseases/infections in

humans and other mammals. Respiratory virus RNA (e.g. mRNA) vaccines can be used as therapeutic or prophylactic agents, alone or in combination with other vaccine(s). They may be used in medicine to prevent and/or treat respiratory disease/infection. In exemplary aspects, the RNA (e.g., mRNA) vaccines of the present disclosure are used to provide prophylactic protection from hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1). Prophylactic protection from hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) can be achieved following administration of a RNA (e.g., mRNA) vaccine of the present disclosure. Respiratory virus RNA (e.g., mRNA) vaccines of the present disclosure may be used to treat or prevent viral "co-infections" containing two or more respiratory infections. Vaccines can be administered once, twice, three times, four times or more, but it is likely sufficient to administer the vaccine once (optionally followed by a single booster). It is possible, although less desirable, to administer the vaccine to an infected individual to achieve a therapeutic response. Dosing may need to be adjusted accordingly.

A method of eliciting an immune response in a subject against hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) is provided in aspects of the present disclosure. The method involves administering to the subject a respiratory virus RNA (e.g., mRNA) vaccine comprising at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) antigenic polypeptide thereof, thereby inducing in the subject an immune response specific to hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) antigenic polypeptide or an immunogenic fragment thereof, wherein anti-antigenic polypeptide antibody titer in the subject is increased following vaccination relative to anti-antigenic polypeptide antibody titer in a subject vaccinated with a prophylactically effective dose of a traditional vaccine against hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1). An "anti-antigenic polypeptide antibody" is a serum antibody the binds specifically to the antigenic polypeptide.

In some embodiments, a RNA (e.g., mRNA) vaccine (e.g., a hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1 RNA vaccine) capable of eliciting an immune response is administered intramuscularly via a composition including a compound according to Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe) (e.g., Compound 3, 18, 20, 25, 26, 29, 30, 60, 108-112, or 122).

A prophylactically effective dose is a therapeutically effective dose that prevents infection with the virus at a clinically acceptable level. In some embodiments the therapeutically effective dose is a dose listed in a package insert for the vaccine. A traditional vaccine, as used herein, refers to a vaccine other than the RNA (e.g., mRNA) vaccines of the present disclosure. For instance, a traditional vaccine includes but is not limited to live/attenuated microorganism vaccines, killed/inactivated microorganism vaccines, subunit vaccines, protein antigen vaccines, DNA vaccines, VLP vaccines, etc. In exemplary embodiments, a traditional vaccine is a vaccine that has achieved regulatory approval and/or is registered by a national drug regulatory body, for example the Food and Drug Administration (FDA) in the United States or the European Medicines Agency (EMA).

In some embodiments the anti-antigenic polypeptide antibody titer in the subject is increased 1 log to 10 log following vaccination relative to anti-antigenic polypeptide antibody titer in a subject vaccinated with a prophylactically effective dose of a traditional vaccine against hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1).

In some embodiments the anti-antigenic polypeptide antibody titer in the subject is increased 1 log, 2 log, 3 log, 5 log or 10 log following vaccination relative to anti-antigenic polypeptide antibody titer in a subject vaccinated with a prophylactically effective dose of a traditional vaccine against hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1).

A method of eliciting an immune response in a subject against hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) is provided in other aspects of the disclosure. The method involves administering to the subject a respiratory virus RNA (e.g., mRNA) vaccine comprising at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) antigenic polypeptide or an immunogenic fragment thereof, thereby inducing in the subject an immune response specific to hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) antigenic polypeptide or an immunogenic fragment thereof, wherein the immune response in the subject is equivalent to an immune response in a subject vaccinated with a traditional vaccine against the hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) at 2 times to 100 times the dosage level relative to the RNA (e.g., mRNA) vaccine.

In some embodiments, the immune response in the subject is equivalent to an immune response in a subject vaccinated with a traditional vaccine at 2, 3, 4, 5, 10, 50, 100 times the dosage level relative to the hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) RNA (e.g., mRNA) vaccine.

In some embodiments the immune response in the subject is equivalent to an immune response in a subject vaccinated with a traditional vaccine at 10-100 times, or 100-1000 times, the dosage level relative to the hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) RNA (e.g., mRNA) vaccine.

In some embodiments the immune response is assessed by determining [protein] antibody titer in the subject.

Some aspects of the present disclosure provide a method of eliciting an immune response in a subject against a In some embodiments the immune response in the subject is equivalent to an immune response in a subject vaccinated with a traditional vaccine at 2, 3, 4, 5, 10, 50, 100 times the dosage level relative to the hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) RNA (e.g., mRNA) vaccine by administering to the subject a respiratory virus RNA (e.g., mRNA) vaccine comprising at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) antigenic polypeptide, thereby inducing in the subject an immune response specific to the antigenic polypeptide or an immunogenic fragment thereof, wherein the immune response in the subject is induced 2 days to 10 weeks earlier relative to an immune response induced in a subject vaccinated with a prophylactically effective dose of a traditional vaccine against the hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1). In some embodiments, the immune response in the subject is induced in a subject vaccinated with a prophylactically effective dose of a traditional vaccine at 2 times to 100 times the dosage level relative to the RNA (e.g., mRNA) vaccine.

In some embodiments, the immune response in the subject is induced 2 days earlier, or 3 days earlier, relative to an immune response induced in a subject vaccinated with a prophylactically effective dose of a traditional vaccine.

In some embodiments the immune response in the subject is induced 1 week, 2 weeks, 3 weeks, 5 weeks, or 10 weeks earlier relative to an immune response induced in a subject vaccinated with a prophylactically effective dose of a traditional vaccine.

Also provided herein is a method of eliciting an immune response in a subject against hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) by administering to the subject a respiratory virus RNA (e.g., mRNA) vaccine having an open reading frame encoding a first antigenic polypeptide, wherein the RNA polynucleotide does not include a stabilization element, and wherein an adjuvant is not co-formulated or co-administered with the vaccine.

Therapeutic and Prophylactic Compositions

Provided herein are compositions (e.g., pharmaceutical compositions), methods, kits and reagents for prevention, treatment or diagnosis of hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) in humans and other mammals, for example. Respiratory virus RNA (e.g. mRNA) vaccines can be used as therapeutic or prophylactic agents. They may be used in medicine to prevent and/or treat infectious disease. In some embodiments, the respiratory RNA (e.g., mRNA) vaccines of the present disclosure are used fin the priming of immune effector cells, for example, to activate peripheral blood mononuclear cells (PBMCs) ex vivo, which are then infused (re-infused) into a subject.

In some embodiments, respiratory virus vaccine containing RNA (e.g., mRNA) polynucleotides as described herein can be administered to a subject (e.g., a mammalian subject, such as a human subject), and the RNA (e.g., mRNA) polynucleotides are translated in vivo to produce an antigenic polypeptide.

The respiratory virus RNA (e.g., mRNA) vaccines may be induced for translation of a polypeptide (e.g., antigen or immunogen) in a cell, tissue or organism. In some embodiments, such translation occurs in vivo, although such translation may occur ex vivo, in culture or in vitro. In some embodiments, the cell, tissue or organism is contacted with an effective amount of a composition containing a respiratory virus RNA (e.g., mRNA) vaccine that contains a polynucleotide that has at least one a translatable region encoding an antigenic polypeptide.

An "effective amount" of an respiratory virus RNA (e.g. mRNA) vaccine is provided based, at least in part, on the target tissue, target cell type, means of administration, physical characteristics of the polynucleotide (e.g., size, and extent of modified nucleosides) and other components of the vaccine, and other determinants. In general, an effective amount of the respiratory virus RNA (e.g., mRNA) vaccine composition provides an induced or boosted immune response as a function of antigen production in the cell, preferably more efficient than a composition containing a corresponding unmodified polynucleotide encoding the same antigen or a peptide antigen. Increased antigen production may be demonstrated by increased cell transfection (the percentage of cells transfected with the RNA, e.g., mRNA, vaccine), increased protein translation from the polynucleotide, decreased nucleic acid degradation (as demonstrated, for example, by increased duration of protein translation from a modified polynucleotide), or altered antigen specific immune response of the host cell.

In some embodiments, RNA (e.g. mRNA) vaccines (including polynucleotides their encoded polypeptides) in accordance with the present disclosure may be used for treatment of hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1).

Respiratory RNA (e.g. mRNA) vaccines may be administered prophylactically or therapeutically as part of an active immunization scheme to healthy individuals or early in infection during the incubation phase or during active infection after onset of symptoms. In some embodiments, the amount of RNA (e.g., mRNA) vaccine of the present disclosure provided to a cell, a tissue or a subject may be an amount effective for immune prophylaxis.

Respiratory virus RNA (e.g. mRNA) vaccines may be administrated with other prophylactic or therapeutic compounds. As a non-limiting example, a prophylactic or therapeutic compound may be an adjuvant or a booster. As used herein, when referring to a prophylactic composition, such as a vaccine, the term "booster" refers to an extra administration of the prophylactic (vaccine) composition. A booster (or booster vaccine) may be given after an earlier administration of the prophylactic composition. The time of administration between the initial administration of the prophylactic composition and the booster may be, but is not limited to, 1 minute, 2 minutes, 3 minutes, 4 minutes, 5 minutes, 6 minutes, 7 minutes, 8 minutes, 9 minutes, 10 minutes, 15 minutes, 20 minutes 35 minutes, 40 minutes, 45 minutes, 50 minutes, 55 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 1 day, 36 hours, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 10 days, 2 weeks, 3 weeks, 1 month, 2 months, 3

months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 18 months, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, 12 years, 13 years, 14 years, 15 years, 16 years, 17 years, 18 years, 19 years, 20 years, 25 years, 30 years, 35 years, 40 years, 45 years, 50 years, 55 years, 60 years, 65 years, 70 years, 75 years, 80 years, 85 years, 90 years, 95 years or more than 99 years. In some embodiments, the time of administration between the initial administration of the prophylactic composition and the booster may be, but is not limited to, 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 6 months or 1 year.

In some embodiments, respiratory virus RNA (e.g. mRNA) vaccines may be administered intramuscularly or intradermally, similarly to the administration of inactivated vaccines known in the art.

Respiratory virus RNA (e.g. mRNA) vaccines may be utilized in various settings depending on the prevalence of the infection or the degree or level of unmet medical need. As a non-limiting example, the RNA (e.g., mRNA) vaccines may be utilized to treat and/or prevent a variety of respiratory infections. RNA (e.g., mRNA) vaccines have superior properties in that they produce much larger antibody titers and produce responses early than commercially available anti-viral agents/compositions.

Provided herein are pharmaceutical compositions including respiratory virus RNA (e.g. mRNA) vaccines and RNA (e.g. mRNA) vaccine compositions and/or complexes optionally in combination with one or more pharmaceutically acceptable excipients.

Respiratory virus RNA (e.g. mRNA) vaccines may be formulated or administered alone or in conjunction with one or more other components. For instance, hMPV/PIV3/RSV RNA (e.g., mRNA) vaccines (vaccine compositions) may comprise other components including, but not limited to, adjuvants.

In some embodiments, respiratory virus (e.g. mRNA) vaccines do not include an adjuvant (they are adjuvant free).

Respiratory virus RNA (e.g. mRNA) vaccines may be formulated or administered in combination with one or more pharmaceutically-acceptable excipients. In some embodiments, vaccine compositions comprise at least one additional active substances, such as, for example, a therapeutically-active substance, a prophylactically-active substance, or a combination of both. Vaccine compositions may be sterile, pyrogen-free or both sterile and pyrogen-free. General considerations in the formulation and/or manufacture of pharmaceutical agents, such as vaccine compositions, may be found, for example, in Remington: The Science and Practice of Pharmacy 21st ed., Lippincott Williams & Wilkins, 2005 (incorporated herein by reference in its entirety).

In some embodiments, respiratory virus RNA (e.g. mRNA) vaccines are administered to humans, human patients or subjects. For the purposes of the present disclosure, the phrase "active ingredient" generally refers to the RNA (e.g., mRNA) vaccines or the polynucleotides contained therein, for example, RNA polynucleotides (e.g., mRNA polynucleotides) encoding antigenic polypeptides.

Formulations of the respiratory virus vaccine compositions described herein may be prepared by any method known or hereafter developed in the art of pharmacology. In general, such preparatory methods include the step of bringing the active ingredient (e.g., mRNA polynucleotide) into association with an excipient and/or one or more other accessory ingredients, and then, if necessary and/or desirable, dividing, shaping and/or packaging the product into a desired single- or multi-dose unit.

Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition in accordance with the disclosure will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100%, e.g., between 0.5 and 50%, between 1-30%, between 5-80%, at least 80% (w/w) active ingredient.

Respiratory virus RNA (e.g. mRNA) vaccines can be formulated using one or more excipients to: (1) increase stability; (2) increase cell transfection; (3) permit the sustained or delayed release (e.g., from a depot formulation); (4) alter the biodistribution (e.g., target to specific tissues or cell types); (5) increase the translation of encoded protein in vivo; and/or (6) alter the release profile of encoded protein (antigen) in vivo. In addition to traditional excipients such as any and all solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, excipients can include, without limitation, lipidoids, liposomes, lipid nanoparticles, polymers, lipoplexes, core-shell nanoparticles, peptides, proteins, cells transfected with respiratory virus RNA (e.g. mRNA) vaccines (e.g., for transplantation into a subject), hyaluronidase, nanoparticle mimics and combinations thereof.

Stabilizing Elements

Naturally-occurring eukaryotic mRNA molecules have been found to contain stabilizing elements, including, but not limited to untranslated regions (UTR) at their 5'-end (5'UTR) and/or at their 3'-end (3'UTR), in addition to other structural features, such as a 5'-cap structure or a 3'-poly(A) tail. Both the 5'UTR and the 3'UTR are typically transcribed from the genomic DNA and are elements of the premature mRNA. Characteristic structural features of mature mRNA, such as the 5'-cap and the 3'-poly(A) tail are usually added to the transcribed (premature) mRNA during mRNA processing. The 3'-poly(A) tail is typically a stretch of adenine nucleotides added to the 3'-end of the transcribed mRNA. It can comprise up to about 400 adenine nucleotides. In some embodiments the length of the 3'-poly(A) tail may be an essential element with respect to the stability of the individual mRNA.

In some embodiments the RNA (e.g., mRNA) vaccine may include one or more stabilizing elements. Stabilizing elements may include for instance a histone stem-loop. A stem-loop binding protein (SLBP), a 32 kDa protein has been identified. It is associated with the histone stem-loop at the 3'-end of the histone messages in both the nucleus and the cytoplasm. Its expression level is regulated by the cell cycle; it peaks during the S-phase, when histone mRNA levels are also elevated. The protein has been shown to be essential for efficient 3'-end processing of histone pre-mRNA by the U7 snRNP. SLBP continues to be associated with the stem-loop after processing, and then stimulates the translation of mature histone mRNAs into histone proteins in the cytoplasm. The RNA binding domain of SLBP is conserved through metazoa and protozoa; its binding to the histone stem-loop depends on the structure of the loop. The minimum binding site includes at least three nucleotides 5' and two nucleotides 3' relative to the stem-loop.

In some embodiments, the RNA (e.g., mRNA) vaccines include a coding region, at least one histone stem-loop, and optionally, a poly(A) sequence or polyadenylation signal.

The poly(A) sequence or polyadenylation signal generally should enhance the expression level of the encoded protein. The encoded protein, in some embodiments, is not a histone protein, a reporter protein (e.g. Luciferase, GFP, EGFP, β-Galactosidase, EGFP), or a marker or selection protein (e.g. alpha-Globin, Galactokinase and Xanthine:guanine phosphoribosyl transferase (GPT)).

In some embodiments, the combination of a poly(A) sequence or polyadenylation signal and at least one histone stem-loop, even though both represent alternative mechanisms in nature, acts synergistically to increase the protein expression beyond the level observed with either of the individual elements. It has been found that the synergistic effect of the combination of poly(A) and at least one histone stem-loop does not depend on the order of the elements or the length of the poly(A) sequence.

In some embodiments, the RNA (e.g., mRNA) vaccine does not comprise a histone downstream element (HDE). "Histone downstream element" (HDE) includes a purine-rich polynucleotide stretch of approximately 15 to 20 nucleotides 3' of naturally occurring stem-loops, representing the binding site for the U7 snRNA, which is involved in processing of histone pre-mRNA into mature histone mRNA. Ideally, the inventive nucleic acid does not include an intron.

In some embodiments, the RNA (e.g., mRNA) vaccine may or may not contain a enhancer and/or promoter sequence, which may be modified or unmodified or which may be activated or inactivated. In some embodiments, the histone stem-loop is generally derived from histone genes, and includes an intramolecular base pairing of two neighbored partially or entirely reverse complementary sequences separated by a spacer, including (e.g., consisting of) a short sequence, which forms the loop of the structure. The unpaired loop region is typically unable to base pair with either of the stem loop elements. It occurs more often in RNA, as is a key component of many RNA secondary structures, but may be present in single-stranded DNA as well. Stability of the stem-loop structure generally depends on the length, number of mismatches or bulges, and base composition of the paired region. In some embodiments, wobble base pairing (non-Watson-Crick base pairing) may result. In some embodiments, the at least one histone stem-loop sequence comprises a length of 15 to 45 nucleotides.

In other embodiments the RNA (e.g., mRNA) vaccine may have one or more AU-rich sequences removed. These sequences, sometimes referred to as AURES are destabilizing sequences found in the 3'UTR. The AURES may be removed from the RNA (e.g., mRNA) vaccines. Alternatively the AURES may remain in the RNA (e.g., mRNA) vaccine.

Nanoparticle Formulations

In some embodiments, respiratory virus RNA (e.g. mRNA) vaccines are formulated in a nanoparticle. In some embodiments, respiratory virus RNA (e.g. mRNA) vaccines are formulated in a lipid nanoparticle. In some embodiments, respiratory virus RNA (e.g. mRNA) vaccines are formulated in a lipid-polycation complex, referred to as a cationic lipid nanoparticle. As a non-limiting example, the polycation may include a cationic peptide or a polypeptide such as, but not limited to, polylysine, polyornithine and/or polyarginine. In some embodiments, respiratory virus RNA (e.g., mRNA) vaccines are formulated in a lipid nanoparticle that includes a non-cationic lipid such as, but not limited to, cholesterol or dioleoyl phosphatidylethanolamine (DOPE).

A lipid nanoparticle formulation may be influenced by, but not limited to, the selection of the cationic lipid component, the degree of cationic lipid saturation, the nature of the PEGylation, ratio of all components and biophysical parameters such as size. In one example by Semple et al. (*Nature Biotech.* 2010 28:172-176), the lipid nanoparticle formulation is composed of 57.1% cationic lipid, 7.1% dipalmitoylphosphatidylcholine, 34.3% cholesterol, and 1.4% PEG-c-DMA. As another example, changing the composition of the cationic lipid can more effectively deliver siRNA to various antigen presenting cells (Basha et al. *Mol Ther.* 2011 19:2186-2200).

In some embodiments, lipid nanoparticle formulations may comprise 35 to 45% cationic lipid, 40% to 50% cationic lipid, 50% to 60% cationic lipid and/or 55% to 65% cationic lipid. In some embodiments, the ratio of lipid to RNA (e.g., mRNA) in lipid nanoparticles may be 5:1 to 20:1, 10:1 to 25:1, 15:1 to 30:1 and/or at least 30:1.

In some embodiments, the ratio of PEG in the lipid nanoparticle formulations may be increased or decreased and/or the carbon chain length of the PEG lipid may be modified from C14 to C18 to alter the pharmacokinetics and/or biodistribution of the lipid nanoparticle formulations. As a non-limiting example, lipid nanoparticle formulations may contain 0.5% to 3.0%, 1.0% to 3.5%, 1.5% to 4.0%, 2.0% to 4.5%, 2.5% to 5.0% and/or 3.0% to 6.0% of the lipid molar ratio of PEG-c-DOMG (R-3-[(ω-methoxy-poly(ethyleneglycol)2000)carbamoyl)]-1,2-dimyristyloxypropyl-3-amine) (also referred to herein as PEG-DOMG) as compared to the cationic lipid, DSPC and cholesterol. In some embodiments, the PEG-c-DOMG may be replaced with a PEG lipid such as, but not limited to, PEG-DSG (1,2-Distearoyl-sn-glycerol, methoxypolyethylene glycol), PEG-DMG (1,2-Dimyristoyl-sn-glycerol) and/or PEG-DPG (1,2-Dipalmitoyl-sn-glycerol, methoxypolyethylene glycol). The cationic lipid may be selected from any lipid known in the art such as, but not limited to, DLin-MC3-DMA, DLin-DMA, C12-200 and DLin-KC2-DMA.

In some embodiments, an respiratory virus RNA (e.g. mRNA) vaccine formulation is a nanoparticle that comprises at least one lipid. The lipid may be selected from, but is not limited to, DLin-DMA, DLin-K-DMA, 98N12-5, C12-200, DLin-MC3-DMA, DLin-KC2-DMA, DODMA, PLGA, PEG, PEG-DMG, PEGylated lipids and amino alcohol lipids. In some embodiments, the lipid may be a cationic lipid such as, but not limited to, DLin-DMA, DLin-D-DMA, DLin-MC3-DMA, DLin-KC2-DMA, DODMA and amino alcohol lipids. The amino alcohol cationic lipid may be the lipids described in and/or made by the methods described in U.S. Patent Publication No. US20130150625, herein incorporated by reference in its entirety. As a non-limiting example, the cationic lipid may be 2-amino-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-2-{[(9Z,2Z)-octadeca-9,12-dien-1-yloxy]methyl}propan-1-ol (Compound 1 in US20130150625); 2-amino-3-[(9Z)-octadec-9-en-1-yloxy]-2-{[(9Z)-octadec-9-en-1-yloxy]methyl}propan-1-ol (Compound 2 in US20130150625); 2-amino-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-2-[(octyloxy)methyl]propan-1-ol (Compound 3 in US20130150625); and 2-(dimethylamino)-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-2-{[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]methyl}propan-1-ol (Compound 4 in US20130150625); or any pharmaceutically acceptable salt or stereoisomer thereof.

Lipid nanoparticle formulations typically comprise a lipid, in particular, an ionizable cationic lipid, for example, 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), or di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319),

and further comprise a neutral lipid, a sterol and a molecule capable of reducing particle aggregation, for example a PEG or PEG-modified lipid.

In some embodiments, a lipid nanoparticle formulation consists essentially of (i) at least one lipid selected from the group consisting of 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy) heptadecanedioate (L319); (ii) a neutral lipid selected from DSPC, DPPC, POPC, DOPE and SM; (iii) a sterol, e.g., cholesterol; and (iv) a PEG-lipid, e.g., PEG-DMG or PEG-cDMA, in a molar ratio of 20-60% cationic lipid:5-25% neutral lipid:25-55% sterol; 0.5-15% PEG-lipid.

In some embodiments, a lipid nanoparticle formulation includes 25% to 75% on a molar basis of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), e.g., 35 to 65%, 45 to 65%, 60%, 57.5%, 50% or 40% on a molar basis.

In some embodiments, a lipid nanoparticle formulation includes 0.5% to 15% on a molar basis of the neutral lipid, e.g., 3 to 12%, 5 to 10% or 15%, 10%, or 7.5% on a molar basis. Examples of neutral lipids include, without limitation, DSPC, POPC, DPPC, DOPE and SM. In some embodiments, the formulation includes 5% to 50% on a molar basis of the sterol (e.g., 15 to 45%, 20 to 40%, 40%, 38.5%, 35%, or 31% on a molar basis. A non-limiting example of a sterol is cholesterol. In some embodiments, a lipid nanoparticle formulation includes 0.5% to 20% on a molar basis of the PEG or PEG-modified lipid (e.g., 0.5 to 10%, 0.5 to 5%, 1.5%, 0.5%, 1.5%, 3.5%, or 5% on a molar basis. In some embodiments, a PEG or PEG modified lipid comprises a PEG molecule of an average molecular weight of 2,000 Da. In some embodiments, a PEG or PEG modified lipid comprises a PEG molecule of an average molecular weight of less than 2,000, for example around 1,500 Da, around 1,000 Da, or around 500 Da. Non-limiting examples of PEG-modified lipids include PEG-distearoyl glycerol (PEG-DMG) (also referred herein as PEG-C14 or C14-PEG), PEG-cDMA (further discussed in Reyes et al. J. Controlled Release, 107, 276-287 (2005) the contents of which are herein incorporated by reference in their entirety).

In some embodiments, lipid nanoparticle formulations include 25-75% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 0.5-15% of the neutral lipid, 5-50% of the sterol, and 0.5-20% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 35-65% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 3-12% of the neutral lipid, 15-45% of the sterol, and 0.5-10% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 45-65% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 5-10% of the neutral lipid, 25-40% of the sterol, and 0.5-10% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 60% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 7.5% of the neutral lipid, 31% of the sterol, and 1.5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 50% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 10% of the neutral lipid, 38.5% of the sterol, and 1.5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 50% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 10% of the neutral lipid, 35% of the sterol, 4.5% or 5% of the PEG or PEG-modified lipid, and 0.5% of the targeting lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 40% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 15% of the neutral lipid, 40% of the sterol, and 5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 57.2% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 7.1% of the neutral lipid, 34.3% of the sterol, and 1.4% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 57.5% of a cationic lipid selected from the PEG lipid is PEG-cDMA (PEG-cDMA is further discussed in Reyes et al. (J. Controlled Release, 107, 276-287 (2005), the contents of which are herein incorporated by reference in their entirety), 7.5% of the neutral lipid, 31.5% of the sterol, and 3.5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations consists essentially of a lipid mixture in molar ratios of 20-70% cationic lipid:5-45% neutral lipid:20-55% cholesterol: 0.5-15% PEG-modified lipid. In some embodiments, lipid nanoparticle formulations consists essentially of a lipid mixture in a molar ratio of 20-60% cationic lipid:5-25% neutral lipid: 25-55% cholesterol: 0.5-15% PEG-modified lipid.

In some embodiments, the molar lipid ratio is 50/10/38.5/1.5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG, PEG-DSG or PEG-DPG), 57.2/7.1134.3/1.4 (mol % cationic lipid/neutral lipid, e.g., DPPC/Chol/PEG-modified lipid, e.g., PEG-cDMA), 40/15/40/5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG), 50/10/35/4.5/0.5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DSG), 50/10/35/5 (cationic

lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG), 40/10/40/10 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG or PEG-cDMA), 35/15/40/10 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG or PEG-cDMA) or 52/13/30/5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG or PEG-cDMA).

Non-limiting examples of lipid nanoparticle compositions and methods of making them are described, for example, in Semple et al. (2010) *Nat. Biotechnol.* 28:172-176; Jayarama et al. (2012), *Angew. Chem. Int. Ed.,* 51: 8529-8533; and Maier et al. (2013) *Molecular Therapy* 21, 1570-1578 (the contents of each of which are incorporated herein by reference in their entirety).

In some embodiments, lipid nanoparticle formulations may comprise a cationic lipid, a PEG lipid and a structural lipid and optionally comprise a non-cationic lipid. As a non-limiting example, a lipid nanoparticle may comprise 40-60% of cationic lipid, 5-15% of a non-cationic lipid, 1-2% of a PEG lipid and 30-50% of a structural lipid. As another non-limiting example, the lipid nanoparticle may comprise 50% cationic lipid, 10% non-cationic lipid, 1.5% PEG lipid and 38.5% structural lipid. As yet another non-limiting example, a lipid nanoparticle may comprise 55% cationic lipid, 10% non-cationic lipid, 2.5% PEG lipid and 32.5% structural lipid. In some embodiments, the cationic lipid may be any cationic lipid described herein such as, but not limited to, DLin-KC2-DMA, DLin-MC3-DMA and L319.

In some embodiments, the lipid nanoparticle formulations described herein may be 4 component lipid nanoparticles. The lipid nanoparticle may comprise a cationic lipid, a non-cationic lipid, a PEG lipid and a structural lipid. As a non-limiting example, the lipid nanoparticle may comprise 40-60% of cationic lipid, 5-15% of a non-cationic lipid, 1-2% of a PEG lipid and 30-50% of a structural lipid. As another non-limiting example, the lipid nanoparticle may comprise 50% cationic lipid, 10% non-cationic lipid, 1.5% PEG lipid and 38.5% structural lipid. As yet another non-limiting example, the lipid nanoparticle may comprise 55% cationic lipid, 10% non-cationic lipid, 2.5% PEG lipid and 32.5% structural lipid. In some embodiments, the cationic lipid may be any cationic lipid described herein such as, but not limited to, DLin-KC2-DMA, DLin-MC3-DMA and L319.

In some embodiments, the lipid nanoparticle formulations described herein may comprise a cationic lipid, a non-cationic lipid, a PEG lipid and a structural lipid. As a non-limiting example, the lipid nanoparticle comprise 50% of the cationic lipid DLin-KC2-DMA, 10% of the non-cationic lipid DSPC, 1.5% of the PEG lipid PEG-DOMG and 38.5% of the structural lipid cholesterol. As a non-limiting example, the lipid nanoparticle comprise 50% of the cationic lipid DLin-MC3-DMA, 10% of the non-cationic lipid DSPC, 1.5% of the PEG lipid PEG-DOMG and 38.5% of the structural lipid cholesterol. As a non-limiting example, the lipid nanoparticle comprise 50% of the cationic lipid DLin-MC3-DMA, 10% of the non-cationic lipid DSPC, 1.5% of the PEG lipid PEG-DMG and 38.5% of the structural lipid cholesterol. As yet another non-limiting example, the lipid nanoparticle comprise 55% of the cationic lipid L319, 10% of the non-cationic lipid DSPC, 2.5% of the PEG lipid PEG-DMG and 32.5% of the structural lipid cholesterol.

Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a vaccine composition may vary, depending upon the identity, size, and/or condition of the subject being treated and further depending upon the route by which the composition is to be administered. For example, the composition may comprise between 0.1% and 99% (w/w) of the active ingredient. By way of example, the composition may comprise between 0.1% and 100%, e.g., between 0.5 and 50%, between 1-30%, between 5-80%, at least 80% (w/w) active ingredient.

In some embodiments, the respiratory virus RNA (e.g. mRNA) vaccine composition may comprise the polynucleotide described herein, formulated in a lipid nanoparticle comprising MC3, Cholesterol, DSPC and PEG2000-DMG, the buffer trisodium citrate, sucrose and water for injection. As a non-limiting example, the composition comprises: 2.0 mg/mL of drug substance (e.g., polynucleotides encoding H10N8 hMPV), 21.8 mg/mL of MC3, 10.1 mg/mL of cholesterol, 5.4 mg/mL of DSPC, 2.7 mg/mL of PEG2000-DMG, 5.16 mg/mL of trisodium citrate, 71 mg/mL of sucrose and 1.0 mL of water for injection.

In some embodiments, a nanoparticle (e.g., a lipid nanoparticle) has a mean diameter of 10-500 nm, 20-400 nm, 30-300 nm, 40-200 nm. In some embodiments, a nanoparticle (e.g., a lipid nanoparticle) has a mean diameter of 50-150 nm, 50-200 nm, 80-100 nm or 80-200 nm.

Liposomes, Lipoplexes, and Lipid Nanoparticles

The RNA (e.g., mRNA) vaccines of the disclosure can be formulated using one or more liposomes, lipoplexes, or lipid nanoparticles. In some embodiments, pharmaceutical compositions of RNA (e.g., mRNA) vaccines include liposomes. Liposomes are artificially-prepared vesicles which may primarily be composed of a lipid bilayer and may be used as a delivery vehicle for the administration of nutrients and pharmaceutical formulations. Liposomes can be of different sizes such as, but not limited to, a multilamellar vesicle (MLV) which may be hundreds of nanometers in diameter and may contain a series of concentric bilayers separated by narrow aqueous compartments, a small unicellular vesicle (SUV) which may be smaller than 50 nm in diameter, and a large unilamellar vesicle (LUV) which may be between 50 and 500 nm in diameter. Liposome design may include, but is not limited to, opsonins or ligands in order to improve the attachment of liposomes to unhealthy tissue or to activate events such as, but not limited to, endocytosis. Liposomes may contain a low or a high pH in order to improve the delivery of the pharmaceutical formulations.

The formation of liposomes may depend on the physicochemical characteristics such as, but not limited to, the pharmaceutical formulation entrapped and the liposomal ingredients, the nature of the medium in which the lipid vesicles are dispersed, the effective concentration of the entrapped substance and its potential toxicity, any additional processes involved during the application and/or delivery of the vesicles, the optimization size, polydispersity and the shelf-life of the vesicles for the intended application, and the batch-to-batch reproducibility and possibility of large-scale production of safe and efficient liposomal products.

In some embodiments, pharmaceutical compositions described herein may include, without limitation, liposomes such as those formed from 1,2-dioleyloxy-N,N-dimethylaminopropane (DODMA) liposomes, DiLa2 liposomes from Marina Biotech (Bothell, Wash.), 1,2-dilinoleyloxy-3-dimethylaminopropane (DLin-DMA), 2,2-dilinoleyl-4-(2-dimethylaminoethyl)-[1,3]-dioxolane (DLin-KC2-DMA), and MC3 (US20100324120; herein incorporated by reference in its entirety) and liposomes which may deliver small

molecule drugs such as, but not limited to, DOXIL® from Janssen Biotech, Inc. (Horsham, Pa.).

In some embodiments, pharmaceutical compositions described herein may include, without limitation, liposomes such as those formed from the synthesis of stabilized plasmid-lipid particles (SPLP) or stabilized nucleic acid lipid particle (SNALP) that have been previously described and shown to be suitable for oligonucleotide delivery in vitro and in vivo (see Wheeler et al. Gene Therapy. 1999 6:271-281; Zhang et al. Gene Therapy. 1999 6:1438-1447; Jeffs et al. Pharm Res. 2005 22:362-372; Morrissey et al., Nat Biotechnol. 2005 2:1002-1007; Zimmermann et al., Nature. 2006 441:111-114; Heyes et al. J Contr Rel. 2005 107:276-287; Semple et al. Nature Biotech. 2010 28:172-176; Judge et al. J Clin Invest. 2009 119:661-673; deFougerolles Hum Gene Ther. 2008 19:125-132; U.S. Patent Publication No US20130122104; all of which are incorporated herein in their entireties). The original manufacture method by Wheeler et al. was a detergent dialysis method, which was later improved by Jeffs et al. and is referred to as the spontaneous vesicle formation method. The liposome formulations are composed of 3 to 4 lipid components in addition to the polynucleotide. As an example a liposome can contain, but is not limited to, 55% cholesterol, 20% disteroylphosphatidyl choline (DSPC), 10% PEG-S-DSG, and 15% 1,2-dioleyloxy-N,N-dimethylaminopropane (DODMA), as described by Jeffs et al. As another example, certain liposome formulations may contain, but are not limited to, 48% cholesterol, 20% DSPC, 2% PEG-c-DMA, and 30% cationic lipid, where the cationic lipid can be 1,2-distearloxy-N,N-dimethylaminopropane (DSDMA), DODMA, DLin-DMA, or 1,2-dilinolenyloxy-3-dimethylaminopropane (DLenDMA), as described by Heyes et al.

In some embodiments, liposome formulations may comprise from about 25.0% cholesterol to about 40.0% cholesterol, from about 30.0% cholesterol to about 45.0% cholesterol, from about 35.0% cholesterol to about 50.0% cholesterol and/or from about 48.5% cholesterol to about 60% cholesterol. In some embodiments, formulations may comprise a percentage of cholesterol selected from the group consisting of 28.5%, 31.5%, 33.5%, 36.5%, 37.0%, 38.5%, 39.0% and 43.5%. In some embodiments, formulations may comprise from about 5.0% to about 10.0% DSPC and/or from about 7.0% to about 15.0% DSPC.

In some embodiments, the RNA (e.g., mRNA) vaccine pharmaceutical compositions may be formulated in liposomes such as, but not limited to, DiLa2 liposomes (Marina Biotech, Bothell, Wash.), SMARTICLES® (Marina Biotech, Bothell, Wash.), neutral DOPC (1,2-dioleoyl-sn-glycero-3-phosphocholine) based liposomes (e.g., siRNA delivery for ovarian cancer (Landen et al. Cancer Biology & Therapy 2006 5(12)1708-1713); herein incorporated by reference in its entirety) and hyaluronan-coated liposomes (Quiet Therapeutics, Israel).

In some embodiments, the cationic lipid may be a low molecular weight cationic lipid such as those described in U.S. Patent Application No. 20130090372, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the RNA (e.g., mRNA) vaccines may be formulated in a lipid vesicle, which may have crosslinks between functionalized lipid bilayers.

In some embodiments, the RNA (e.g., mRNA) vaccines may be formulated in a lipid-polycation complex. The formation of the lipid-polycation complex may be accomplished by methods known in the art and/or as described in U.S. Pub. No. 20120178702, herein incorporated by reference in its entirety. As a non-limiting example, the polycation may include a cationic peptide or a polypeptide such as, but not limited to, polylysine, polyornithine and/or polyarginine. In some embodiments, the RNA (e.g., mRNA) vaccines may be formulated in a lipid-polycation complex, which may further include a non-cationic lipid such as, but not limited to, cholesterol or dioleoyl phosphatidylethanolamine (DOPE).

In some embodiments, the ratio of PEG in the lipid nanoparticle (LNP) formulations may be increased or decreased and/or the carbon chain length of the PEG lipid may be modified from C14 to C18 to alter the pharmacokinetics and/or biodistribution of the LNP formulations. As a non-limiting example, LNP formulations may contain from about 0.5% to about 3.0%, from about 1.0% to about 3.5%, from about 1.5% to about 4.0%, from about 2.0% to about 4.5%, from about 2.5% to about 5.0% and/or from about 3.0% to about 6.0% of the lipid molar ratio of PEG-c-DOMG (R-3-[(ω-methoxy-poly(ethyleneglycol) 2000)carbamoyl)]-1,2-dimyristyloxypropyl-3-amine) (also referred to herein as PEG-DOMG) as compared to the cationic lipid, DSPC and cholesterol. In some embodiments, the PEG-c-DOMG may be replaced with a PEG lipid such as, but not limited to, PEG-DSG (1,2-Distearoyl-sn-glycerol, methoxypolyethylene glycol), PEG-DMG (1,2-Dimyristoyl-sn-glycerol) and/or PEG-DPG (1,2-Dipalmitoyl-sn-glycerol, methoxypolyethylene glycol). The cationic lipid may be selected from any lipid known in the art such as, but not limited to, DLin-MC3-DMA, DLin-DMA, C12-200 and DLin-KC2-DMA.

In some embodiments, the RNA (e.g., mRNA) vaccines may be formulated in a lipid nanoparticle.

In some embodiments, the RNA (e.g., mRNA) vaccine formulation comprising the polynucleotide is a nanoparticle which may comprise at least one lipid. The lipid may be selected from, but is not limited to, DLin-DMA, DLin-K-DMA, 98N12-5, C12-200, DLin-MC3-DMA, DLin-KC2-DMA, DODMA, PLGA, PEG, PEG-DMG, PEGylated lipids and amino alcohol lipids. In another aspect, the lipid may be a cationic lipid such as, but not limited to, DLin-DMA, DLin-D-DMA, DLin-MC3-DMA, DLin-KC2-DMA, DODMA and amino alcohol lipids. The amino alcohol cationic lipid may be the lipids described in and/or made by the methods described in U.S. Patent Publication No. US20130150625, herein incorporated by reference in its entirety. As a non-limiting example, the cationic lipid may be 2-amino-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-2-{[(9Z,2Z)-octadeca-9,12-dien-1-yloxy]methyl}propan-1-ol (Compound 1 in US20130150625); 2-amino-3-[(9Z)-octadec-9-en-1-yloxy]-2-{[(9Z)-octadec-9-en-1-yloxy]methyl}propan-1-ol (Compound 2 in US20130150625); 2-amino-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-2-[(octyloxy)methyl]propan-1-ol (Compound 3 in US20130150625); and 2-(dimethylamino)-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-2-{[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]methyl}propan-1-ol (Compound 4 in US20130150625); or any pharmaceutically acceptable salt or stereoisomer thereof.

Lipid nanoparticle formulations typically comprise a lipid, in particular, an ionizable cationic lipid, for example, 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), or di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), and further comprise a neutral lipid, a sterol and a molecule capable of reducing particle aggregation, for example a PEG or PEG-modified lipid.

In some embodiments, the lipid nanoparticle formulation consists essentially of (i) at least one lipid selected from the group consisting of 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy) heptadecanedioate (L319); (ii) a neutral lipid selected from DSPC, DPPC, POPC, DOPE and SM; (iii) a sterol, e.g., cholesterol; and (iv) a PEG-lipid, e.g., PEG-DMG or PEG-cDMA, in a molar ratio of about 20-60% cationic lipid:5-25% neutral lipid:25-55% sterol; 0.5-15% PEG-lipid.

In some embodiments, the formulation includes from about 25% to about 75% on a molar basis of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), e.g., from about 35 to about 65%, from about 45 to about 65%, about 60%, about 57.5%, about 50% or about 40% on a molar basis.

In some embodiments, the formulation includes from about 0.5% to about 15% on a molar basis of the neutral lipid e.g., from about 3 to about 12%, from about 5 to about 10% or about 15%, about 10%, or about 7.5% on a molar basis. Examples of neutral lipids include, but are not limited to, DSPC, POPC, DPPC, DOPE and SM. In some embodiments, the formulation includes from about 5% to about 50% on a molar basis of the sterol (e.g., about 15 to about 45%, about 20 to about 40%, about 40%, about 38.5%, about 35%, or about 31% on a molar basis. An exemplary sterol is cholesterol. In some embodiments, the formulation includes from about 0.5% to about 20% on a molar basis of the PEG or PEG-modified lipid (e.g., about 0.5 to about 10%, about 0.5 to about 5%, about 1.5%, about 0.5%, about 1.5%, about 3.5%, or about 5% on a molar basis. In some embodiments, the PEG or PEG modified lipid comprises a PEG molecule of an average molecular weight of 2,000 Da. In other embodiments, the PEG or PEG modified lipid comprises a PEG molecule of an average molecular weight of less than 2,000, for example around 1,500 Da, around 1,000 Da, or around 500 Da. Examples of PEG-modified lipids include, but are not limited to, PEG-distearoyl glycerol (PEG-DMG) (also referred herein as PEG-C14 or C14-PEG), PEG-cDMA (further discussed in Reyes et al. *J. Controlled Release,* 107, 276-287 (2005) the contents of which are herein incorporated by reference in their entirety)

In some embodiments, the formulations of the present disclosure include 25-75% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 0.5-15% of the neutral lipid, 5-50% of the sterol, and 0.5-20% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include 35-65% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 3-12% of the neutral lipid, 15-45% of the sterol, and 0.5-10% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include 45-65% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 5-10% of the neutral lipid, 25-40% of the sterol, and 0.5-10% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include about 60% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 7.5% of the neutral lipid, about 31% of the sterol, and about 1.5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include about 50% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 10% of the neutral lipid, about 38.5% of the sterol, and about 1.5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include about 50% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 10% of the neutral lipid, about 35% of the sterol, about 4.5% or about 5% of the PEG or PEG-modified lipid, and about 0.5% of the targeting lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include about 40% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 15% of the neutral lipid, about 40% of the sterol, and about 5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include about 57.2% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 7.1% of the neutral lipid, about 34.3% of the sterol, and about 1.4% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include about 57.5% of a cationic lipid selected from the PEG lipid is PEG-cDMA (PEG-cDMA is further discussed in Reyes et al. (J. Controlled Release, 107, 276-287 (2005), the contents of which are herein incorporated by reference in their entirety), about 7.5% of the neutral lipid, about 31.5% of the sterol, and about 3.5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulation consists essentially of a lipid mixture in molar ratios of about 20-70% cationic lipid:5-45% neutral lipid:20-55% cholesterol: 0.5-15% PEG-modified lipid; more preferably in a molar ratio of about 20-60% cationic lipid:5-25% neutral lipid:25-55% cholesterol: 0.5-15% PEG-modified lipid.

In some embodiments, the molar lipid ratio is approximately 50/10/38.5/1.5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG, PEG-DSG or PEG-DPG), 57.2/7.1134.3/1.4 (mol % cationic lipid/neutral lipid, e.g., DPPC/Chol/PEG-modified lipid,

e.g., PEG-cDMA), 40/15/40/5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG), 50/10/35/4.5/0.5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DSG), 50/10/35/5 (cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG), 40/10/40/10 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG or PEG-cDMA), 35/15/40/10 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG or PEG-cDMA) or 52/13/30/5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG or PEG-cDMA).

Examples of lipid nanoparticle compositions and methods of making same are described, for example, in Semple et al. (2010) *Nat. Biotechnol.* 28:172-176; Jayarama et al. (2012), *Angew. Chem. Int. Ed.,* 51: 8529-8533; and Maier et al. (2013) *Molecular Therapy* 21, 1570-1578 (the contents of each of which are incorporated herein by reference in their entirety).

In some embodiments, the lipid nanoparticle formulations described herein may comprise a cationic lipid, a PEG lipid and a structural lipid and optionally comprise a non-cationic lipid. As a non-limiting example, the lipid nanoparticle may comprise about 40-60% of cationic lipid, about 5-15% of a non-cationic lipid, about 1-2% of a PEG lipid and about 30-50% of a structural lipid. As another non-limiting example, the lipid nanoparticle may comprise about 50% cationic lipid, about 10% non-cationic lipid, about 1.5% PEG lipid and about 38.5% structural lipid. As yet another non-limiting example, the lipid nanoparticle may comprise about 55% cationic lipid, about 10% non-cationic lipid, about 2.5% PEG lipid and about 32.5% structural lipid. In some embodiments, the cationic lipid may be any cationic lipid described herein such as, but not limited to, DLin-KC2-DMA, DLin-MC3-DMA and L319.

In some embodiments, the lipid nanoparticle formulations described herein may be 4 component lipid nanoparticles. The lipid nanoparticle may comprise a cationic lipid, a non-cationic lipid, a PEG lipid and a structural lipid. As a non-limiting example, the lipid nanoparticle may comprise about 40-60% of cationic lipid, about 5-15% of a non-cationic lipid, about 1-2% of a PEG lipid and about 30-50% of a structural lipid. As another non-limiting example, the lipid nanoparticle may comprise about 50% cationic lipid, about 10% non-cationic lipid, about 1.5% PEG lipid and about 38.5% structural lipid. As yet another non-limiting example, the lipid nanoparticle may comprise about 55% cationic lipid, about 10% non-cationic lipid, about 2.5% PEG lipid and about 32.5% structural lipid. In some embodiments, the cationic lipid may be any cationic lipid described herein such as, but not limited to, DLin-KC2-DMA, DLin-MC3-DMA and L319.

In some embodiments, the lipid nanoparticle formulations described herein may comprise a cationic lipid, a non-cationic lipid, a PEG lipid and a structural lipid. As a non-limiting example, the lipid nanoparticle comprise about 50% of the cationic lipid DLin-KC2-DMA, about 10% of the non-cationic lipid DSPC, about 1.5% of the PEG lipid PEG-DOMG and about 38.5% of the structural lipid cholesterol. As a non-limiting example, the lipid nanoparticle comprise about 50% of the cationic lipid DLin-MC3-DMA, about 10% of the non-cationic lipid DSPC, about 1.5% of the PEG lipid PEG-DOMG and about 38.5% of the structural lipid cholesterol. As a non-limiting example, the lipid nanoparticle comprise about 50% of the cationic lipid DLin-MC3-DMA, about 10% of the non-cationic lipid DSPC, about 1.5% of the PEG lipid PEG-DMG and about 38.5% of the structural lipid cholesterol. As yet another non-limiting example, the lipid nanoparticle comprise about 55% of the cationic lipid L319, about 10% of the non-cationic lipid DSPC, about 2.5% of the PEG lipid PEG-DMG and about 32.5% of the structural lipid cholesterol.

As a non-limiting example, the cationic lipid may be selected from (20Z,23Z)—N,N-dimethylnonacosa-20,23-dien-10-amine, (17Z,20Z)—N,N-dimemylhexacosa-17,20-dien-9-amine, (1Z,19Z)—N5N-dimethylpentacosa-16,19-dien-8-amine, (13Z,16Z)—N,N-dimethyldocosa-13,16-dien-5-amine, (12Z,15Z)—N,N-dimethylhenicosa-12,15-dien-4-amine, (14Z,17Z)—N,N-dimethyltricosa-14,17-dien-6-amine, (15Z,18Z)—N,N-dimethyltetracosa-15,18-dien-7-amine, (18Z,21Z)—N,N-dimethylheptacosa-18,21-dien-10-amine, (15Z,18Z)—N,N-dimethyltetracosa-15,18-dien-5-amine, (14Z,17Z)—N,N-dimethyltricosa-14,17-dien-4-amine, (19Z,22Z)—N,N-dimeihyloctacosa-19,22-dien-9-amine, (18Z,21 Z)—N,N-dimethylheptacosa-18,21-dien-8 amine, (17Z,20Z)—N,N-dimethylhexacosa-17,20-dien-7-amine, (16Z,19Z)—N,N-dimethylpentacosa-16,19-dien-6-amine, (22Z,25Z)—N,N-dimethylhentriaconta-22,25-dien-10-amine, (21 Z,24Z)—N,N-dimethyltriaconta-21,24-dien-9-amine, (18Z)—N,N-dimetylheptacos-18-en-10-amine, (17Z)—N,N-dimethylhexacos-17-en-9-amine, (19Z,22Z)—N,N-dimethyloctacosa-19,22-dien-7-amine, N,N-dimethylheptacosan-10-amine, (20Z,23Z)—N-ethyl-N-methylnonacosa-20,23-dien-10-amine, 1-[(11Z,14Z)-1-nonylicosa-11,14-dien-1-yl]pyrrolidine, (20Z)—N,N-dimethylheptacos-20-en-10-amine, (15Z)—N,N-dimethyl eptacos-15-en-10-amine, (14Z)—N,N-dimethylnonacos-14-en-10-amine, (17Z)—N,N-dimethylnonacos-17-en-10-amine, (24Z)—N,N-dimethyltritriacont-24-en-10-amine, (20Z)—N,N-dimethylnonacos-20-en-10-amine, (22Z)—N,N-dimethylhentriacont-22-en-10-amine, (16Z)—N,N-dimethylpentacos-16-en-8-amine, (12Z,15Z)—N,N-dimethyl-2-nonylhenicosa-12,15-dien-1-amine, (13Z,16Z)—N,N-dimethyl-3-nonyldocosa-13,16-dien-1 amine, N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]eptadecan-8-amine, 1-[(1S,2R)-2-hexylcyclopropyl]-N,N-dimethylnonadecan-10-amine, N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]nonadecan-10-amine, N,N-dimethyl-21-[(1S,2R)-2-octylcyclopropyl]henicosan-10-amine, N,N-dimethyl-1-[(1S,2S)-2-{[(1R,2R)-2-pentylcyclopropyl]methyl}cyclopropyl]nonadecan-10-amine,N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]hexadecan-8-amine, N,N-dimethyl-[(1R,2S)-2-undecylcyclopropyl]tetradecan-5-amine, N,N-dimethyl-3-{7-[(1S,2R)-2-octylcyclopropyl]heptyl}dodecan-1-amine, 1-[(1R,2S)-2-heptylcyclopropyl]-N,N-dimethyloctadecan-9-amine, 1-[(1S,2R)-2-decylcyclopropyl]-N,N-dimethylpentadecan-6-amine, N,N-dimethyl-1-R1S,2R)-2-octylcyclopropyllpentadecan-8-amine, R—N,N-dimethyl-1-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-3-(octyloxy)propan-2-amine, S—N,N-dimethyl-1-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-3-(octyloxy) propan-2-amine, 1-{2-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-1-[(octyloxy)methyl]ethyl}pyrrolidine, (2S)—N,N-dimethyl-1-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-3-[(5Z)-oct-5-en-1-yloxy]propan-2-amine, 1-{2-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-1-[(octyloxy)methyl] ethyl}azetidine, (2S)-1-(hexyloxy)-N,N-dimethyl-3-R9Z,12Z)-octadeca-9,12-dien-1-yloxylpropan-2-amine, (2S)-1-(heptyloxy)-N,N-dimethyl-3-R9Z,12Z)-octadeca-9,12-dien-1-yloxylpropan-2-amine, N,N-dimethyl-1-(nonyloxy)-3-R9Z,12Z)-octadeca-9,12-dien-1-yloxylpropan-2-amine, N,N-dimethyl-1-[(9Z)-octadec-9-en-1-yloxy]-3-(octyloxy) propan-2-amine; (2S)-N,N-dimethyl-1-[(6Z,9Z,12Z)-octadeca-6,9,12-trien-1-yloxy]-3-(octyloxy)propan-2-amine,

(2S)-1-[(11Z,14Z)-icosa-11,14-dien-1-yloxy]-N,N-dimethyl-3-(pentyloxy)propan-2-amine, (2S)-1-(hexyloxy)-3-[(11Z,14Z)-icosa-11,14-dien-1-yloxy]-N,N-dimethylpropan-2-amine, 1-[(11Z,14Z)-icosa-11,14-dien-1-yloxy]-N,N-dimethyl-3-(octyloxy)propan-2-amine, 1-[(13Z,16Z)-docosa-13,16-dien-1-yloxy]-N,N-dimethyl-3-(octyloxy) propan-2-amine, (2S)-1-[(13Z,16Z)-docosa-13,16-dien-1-yloxy]-3-(hexyloxy)-N,N-dimethylpropan-2-amine, (2S)-1-[(13Z)-docos-13-en-1-yloxy]-3-(hexyloxy)-N,N-dimethylpropan-2-amine, 1-[(13Z)-docos-13-en-1-yloxy]-N,N-dimethyl-3-(octyloxy)propan-2-amine, 1-[(9Z)-hexadec-9-en-1-yloxy]-N,N-dimethyl-3-(octyloxy)propan-2-amine, (2R)-N,N-dimethyl-H(1-metoyloctyl)oxy]-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]propan-2-amine, (2R)-1-[(3,7-dimethyloctyl)oxy]-N,N-dimethyl-3-R9Z,12Z)-octadeca-9,12-dien-1-yloxylpropan-2-amine, N,N-dimethyl-1-(octyloxy)-3-({8-R1S,25)-2-{[(1R,2R)-2-pentylcyclopropyl]methyl}cyclopropyl]octyl}oxy)propan-2-amine, N,N-dimethyl-1-1 [8-(2-oc1ylcyclopropyl)octyl] oxy}-3-(octyloxy)propan-2-amine and (11E,20Z,23Z)—N, N-dimethylnonacosa-11,20,2-trien-10-amine or a pharmaceutically acceptable salt or stereoisomer thereof.

In some embodiments, the LNP formulations of the RNA (e.g., mRNA) vaccines may contain PEG-c-DOMG at 3% lipid molar ratio. In some embodiments, the LNP formulations of the RNA (e.g., mRNA) vaccines may contain PEG-c-DOMG at 1.5% lipid molar ratio.

In some embodiments, the pharmaceutical compositions of the RNA (e.g., mRNA) vaccines may include at least one of the PEGylated lipids described in International Publication No. WO2012099755, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the LNP formulation may contain PEG-DMG 2000 (1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000). In some embodiments, the LNP formulation may contain PEG-DMG 2000, a cationic lipid known in the art and at least one other component. In some embodiments, the LNP formulation may contain PEG-DMG 2000, a cationic lipid known in the art, DSPC and cholesterol. As a non-limiting example, the LNP formulation may contain PEG-DMG 2000, DLin-DMA, DSPC and cholesterol. As another non-limiting example the LNP formulation may contain PEG-DMG 2000, DLin-DMA, DSPC and cholesterol in a molar ratio of 2:40:10:48 (see e.g., Geall et al., Nonviral delivery of self-amplifying RNA (e.g., mRNA) vaccines, PNAS 2012; PMID: 22908294, the contents of each of which are herein incorporated by reference in their entirety).

The lipid nanoparticles described herein may be made in a sterile environment.

In some embodiments, the LNP formulation may be formulated in a nanoparticle such as a nucleic acid-lipid particle. As a non-limiting example, the lipid particle may comprise one or more active agents or therapeutic agents; one or more cationic lipids comprising from about 50 mol % to about 85 mol % of the total lipid present in the particle; one or more non-cationic lipids comprising from about 13 mol % to about 49.5 mol % of the total lipid present in the particle; and one or more conjugated lipids that inhibit aggregation of particles comprising from about 0.5 mol % to about 2 mol % of the total lipid present in the particle.

The nanoparticle formulations may comprise a phosphate conjugate. The phosphate conjugate may increase in vivo circulation times and/or increase the targeted delivery of the nanoparticle. As a non-limiting example, the phosphate conjugates may include a compound of any one of the formulas described in International Application No. WO2013033438, the contents of which are herein incorporated by reference in its entirety.

The nanoparticle formulation may comprise a polymer conjugate. The polymer conjugate may be a water soluble conjugate. The polymer conjugate may have a structure as described in U.S. Patent Application No. 20130059360, the contents of which are herein incorporated by reference in its entirety. In some embodiments, polymer conjugates with the polynucleotides of the present disclosure may be made using the methods and/or segmented polymeric reagents described in U.S. Patent Application No. 20130072709, the contents of which are herein incorporated by reference in its entirety. In some embodiments, the polymer conjugate may have pendant side groups comprising ring moieties such as, but not limited to, the polymer conjugates described in U.S. Patent Publication No. US20130196948, the contents which are herein incorporated by reference in its entirety.

The nanoparticle formulations may comprise a conjugate to enhance the delivery of nanoparticles of the present disclosure in a subject. Further, the conjugate may inhibit phagocytic clearance of the nanoparticles in a subject. In one aspect, the conjugate may be a "self" peptide designed from the human membrane protein CD47 (e.g., the "self" particles described by Rodriguez et al. (*Science* 2013 339, 971-975), herein incorporated by reference in its entirety). As shown by Rodriguez et al., the self peptides delayed macrophage-mediated clearance of nanoparticles which enhanced delivery of the nanoparticles. In another aspect, the conjugate may be the membrane protein CD47 (e.g., see Rodriguez et al. *Science* 2013 339, 971-975, herein incorporated by reference in its entirety). Rodriguez et al. showed that, similarly to "self" peptides, CD47 can increase the circulating particle ratio in a subject as compared to scrambled peptides and PEG coated nanoparticles.

In some embodiments, the RNA (e.g., mRNA) vaccines of the present disclosure are formulated in nanoparticles which comprise a conjugate to enhance the delivery of the nanoparticles of the present disclosure in a subject. The conjugate may be the CD47 membrane or the conjugate may be derived from the CD47 membrane protein, such as the "self" peptide described previously. In some embodiments, the nanoparticle may comprise PEG and a conjugate of CD47 or a derivative thereof. In some embodiments, the nanoparticle may comprise both the "self" peptide described above and the membrane protein CD47.

In some embodiments, a "self" peptide and/or CD47 protein may be conjugated to a virus-like particle or pseudovirion, as described herein for delivery of the RNA (e.g., mRNA) vaccines of the present disclosure.

In some embodiments, RNA (e.g., mRNA) vaccine pharmaceutical compositions comprising the polynucleotides of the present disclosure and a conjugate that may have a degradable linkage. Non-limiting examples of conjugates include an aromatic moiety comprising an ionizable hydrogen atom, a spacer moiety, and a water-soluble polymer. As a non-limiting example, pharmaceutical compositions comprising a conjugate with a degradable linkage and methods for delivering such pharmaceutical compositions are described in U.S. Patent Publication No. US20130184443, the contents of which are herein incorporated by reference in their entirety.

The nanoparticle formulations may be a carbohydrate nanoparticle comprising a carbohydrate carrier and a RNA (e.g., mRNA) vaccine. As a non-limiting example, the carbohydrate carrier may include, but is not limited to, an anhydride-modified phytoglycogen or glycogen-type material, phtoglycogen octenyl succinate, phytoglycogen beta-

dextrin, anhydride-modified phytoglycogen beta-dextrin. (See e.g., International Publication No. WO2012109121; the contents of which are herein incorporated by reference in their entirety).

Nanoparticle formulations of the present disclosure may be coated with a surfactant or polymer in order to improve the delivery of the particle. In some embodiments, the nanoparticle may be coated with a hydrophilic coating such as, but not limited to, PEG coatings and/or coatings that have a neutral surface charge. The hydrophilic coatings may help to deliver nanoparticles with larger payloads such as, but not limited to, RNA (e.g., mRNA) vaccines within the central nervous system. As a non-limiting example nanoparticles comprising a hydrophilic coating and methods of making such nanoparticles are described in U.S. Patent Publication No. US20130183244, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the lipid nanoparticles of the present disclosure may be hydrophilic polymer particles. Non-limiting examples of hydrophilic polymer particles and methods of making hydrophilic polymer particles are described in U.S. Patent Publication No. US20130210991, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the lipid nanoparticles of the present disclosure may be hydrophobic polymer particles.

Lipid nanoparticle formulations may be improved by replacing the cationic lipid with a biodegradable cationic lipid which is known as a rapidly eliminated lipid nanoparticle (reLNP). Ionizable cationic lipids, such as, but not limited to, DLinDMA, DLin-KC2-DMA, and DLin-MC3-DMA, have been shown to accumulate in plasma and tissues over time and may be a potential source of toxicity. The rapid metabolism of the rapidly eliminated lipids can improve the tolerability and therapeutic index of the lipid nanoparticles by an order of magnitude from a 1 mg/kg dose to a 10 mg/kg dose in rat. Inclusion of an enzymatically degraded ester linkage can improve the degradation and metabolism profile of the cationic component, while still maintaining the activity of the reLNP formulation. The ester linkage can be internally located within the lipid chain or it may be terminally located at the terminal end of the lipid chain. The internal ester linkage may replace any carbon in the lipid chain.

In some embodiments, the internal ester linkage may be located on either side of the saturated carbon.

In some embodiments, an immune response may be elicited by delivering a lipid nanoparticle which may include a nanospecies, a polymer and an immunogen. (U.S. Publication No. 20120189700 and International Publication No. WO2012099805; each of which is herein incorporated by reference in their entirety). The polymer may encapsulate the nanospecies or partially encapsulate the nanospecies. The immunogen may be a recombinant protein, a modified RNA and/or a polynucleotide described herein. In some embodiments, the lipid nanoparticle may be formulated for use in a vaccine such as, but not limited to, against a pathogen.

Lipid nanoparticles may be engineered to alter the surface properties of particles so the lipid nanoparticles may penetrate the mucosal barrier. Mucus is located on mucosal tissue such as, but not limited to, oral (e.g., the buccal and esophageal membranes and tonsil tissue), ophthalmic, gastrointestinal (e.g., stomach, small intestine, large intestine, colon, rectum), nasal, respiratory (e.g., nasal, pharyngeal, tracheal and bronchial membranes), genital (e.g., vaginal, cervical and urethral membranes). Nanoparticles larger than 10-200 nm which are preferred for higher drug encapsulation efficiency and the ability to provide the sustained delivery of a wide array of drugs have been thought to be too large to rapidly diffuse through mucosal barriers. Mucus is continuously secreted, shed, discarded or digested and recycled so most of the trapped particles may be removed from the mucosa tissue within seconds or within a few hours. Large polymeric nanoparticles (200 nm-500 nm in diameter) which have been coated densely with a low molecular weight polyethylene glycol (PEG) diffused through mucus only 4 to 6-fold lower than the same particles diffusing in water (Lai et al. PNAS 2007 104(5):1482-487; Lai et al. *Adv Drug Deliv Rev.* 2009 61(2): 158-171; each of which is herein incorporated by reference in their entirety). The transport of nanoparticles may be determined using rates of permeation and/or fluorescent microscopy techniques including, but not limited to, fluorescence recovery after photobleaching (FRAP) and high resolution multiple particle tracking (MPT). As a non-limiting example, compositions which can penetrate a mucosal barrier may be made as described in U.S. Pat. No. 8,241,670 or International Patent Publication No. WO2013110028, the contents of each of which are herein incorporated by reference in its entirety.

The lipid nanoparticle engineered to penetrate mucus may comprise a polymeric material (i.e. a polymeric core) and/or a polymer-vitamin conjugate and/or a tri-block co-polymer. The polymeric material may include, but is not limited to, polyamines, polyethers, polyamides, polyesters, polycarbamates, polyureas, polycarbonates, poly(styrenes), polyimides, polysulfones, polyurethanes, polyacetylenes, polyethylenes, polyethyeneimines, polyisocyanates, polyacrylates, polymethacrylates, polyacrylonitriles, and polyarylates. The polymeric material may be biodegradable and/or biocompatible. Non-limiting examples of biocompatible polymers are described in International Patent Publication No. WO2013116804, the contents of which are herein incorporated by reference in their entirety. The polymeric material may additionally be irradiated. As a non-limiting example, the polymeric material may be gamma irradiated (see e.g., International App. No. WO201282165, herein incorporated by reference in its entirety). Non-limiting examples of specific polymers include poly(caprolactone) (PCL), ethylene vinyl acetate polymer (EVA), poly(lactic acid) (PLA), poly(L-lactic acid) (PLLA), poly(glycolic acid) (PGA), poly (lactic acid-co-glycolic acid) (PLGA), poly(L-lactic acid-co-glycolic acid) (PLLGA), poly(D,L-lactide) (PDLA), poly (L-lactide) (PLLA), poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-caprolactone-co-glycolide), poly(D,L-lactide-co-PEO-co-D,L-lactide), poly(D,L-lactide-co-PPO-co-D,L-lactide), polyalkyl cyanoacralate, polyurethane, poly-L-lysine (PLL), hydroxypropyl methacrylate (HPMA), polyethyleneglycol, poly-L-glutamic acid, poly(hydroxy acids), polyanhydrides, polyorthoesters, poly(ester amides), polyamides, poly(ester ethers), polycarbonates, polyalkylenes such as polyethylene and polypropylene, polyalkylene glycols such as poly(ethylene glycol) (PEG), polyalkylene oxides (PEO), polyalkylene terephthalates such as poly(ethylene terephthalate), polyvinyl alcohols (PVA), polyvinyl ethers, polyvinyl esters such as poly(vinyl acetate), polyvinyl halides such as poly(vinyl chloride) (PVC), polyvinylpyrrolidone, polysiloxanes, polystyrene (PS), polyurethanes, derivatized celluloses such as alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, hydroxypropylcellulose, carboxymethylcellulose, polymers of acrylic acids, such as poly(methyl(meth)acrylate) (PMMA), poly(ethyl(meth)

acrylate), poly(butyl(meth)acrylate), poly(isobutyl(meth) acrylate), poly(hexyl(meth)acrylate), poly(isodecyl(meth) acrylate), poly(lauryl(meth)acrylate), poly(phenyl(meth) acrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate) and copolymers and mixtures thereof, polydioxanone and its copolymers, polyhydroxyalkanoates, polypropylene fumarate, polyoxymethylene, poloxamers, poly(ortho)esters, poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), PEG-PLGA-PEG and trimethylene carbonate, polyvinylpyrrolidone. The lipid nanoparticle may be coated or associated with a co-polymer such as, but not limited to, a block co-polymer (such as a branched polyether-polyamide block copolymer described in International Publication No. WO2013012476, herein incorporated by reference in its entirety), and (poly(ethylene glycol))-(poly(propylene oxide))-(poly(ethylene glycol)) triblock copolymer (see e.g., U.S. Publication 20120121718 and U.S. Publication 20100003337 and U.S. Pat. No. 8,263,665, the contents of each of which is herein incorporated by reference in their entirety). The co-polymer may be a polymer that is generally regarded as safe (GRAS) and the formation of the lipid nanoparticle may be in such a way that no new chemical entities are created. For example, the lipid nanoparticle may comprise poloxamers coating PLGA nanoparticles without forming new chemical entities which are still able to rapidly penetrate human mucus (Yang et al. Angew. Chem. Int. Ed. 2011 50:2597-2600; the contents of which are herein incorporated by reference in their entirety). A non-limiting scalable method to produce nanoparticles which can penetrate human mucus is described by Xu et al. (see, e.g., J Control Release 2013, 170(2):279-86; the contents of which are herein incorporated by reference in their entirety).

The vitamin of the polymer-vitamin conjugate may be vitamin E. The vitamin portion of the conjugate may be substituted with other suitable components such as, but not limited to, vitamin A, vitamin E, other vitamins, cholesterol, a hydrophobic moiety, or a hydrophobic component of other surfactants (e.g., sterol chains, fatty acids, hydrocarbon chains and alkylene oxide chains).

The lipid nanoparticle engineered to penetrate mucus may include surface altering agents such as, but not limited to, polynucleotides, anionic proteins (e.g., bovine serum albumin), surfactants (e.g., cationic surfactants such as for example dimethyldioctadecylammonium bromide), sugars or sugar derivatives (e.g., cyclodextrin), nucleic acids, polymers (e.g., heparin, polyethylene glycol and poloxamer), mucolytic agents (e.g., N-acetylcysteine, mugwort, bromelain, papain, clerodendrum, acetylcysteine, bromhexine, carbocisteine, eprazinone, mesna, ambroxol, sobrerol, domiodol, letosteine, stepronin, tiopronin, gelsolin, thymosin β4 dornase alfa, neltenexine, erdosteine) and various DNases including rhDNase. The surface altering agent may be embedded or enmeshed in the particle's surface or disposed (e.g., by coating, adsorption, covalent linkage, or other process) on the surface of the lipid nanoparticle. (see e.g., U.S. Publication 20100215580 and U.S. Publication 20080166414 and US20130164343; the contents of each of which are herein incorporated by reference in their entirety).

In some embodiments, the mucus penetrating lipid nanoparticles may comprise at least one polynucleotide described herein. The polynucleotide may be encapsulated in the lipid nanoparticle and/or disposed on the surface of the particle. The polynucleotide may be covalently coupled to the lipid nanoparticle. Formulations of mucus penetrating lipid nanoparticles may comprise a plurality of nanoparticles. Further, the formulations may contain particles which may interact with the mucus and alter the structural and/or adhesive properties of the surrounding mucus to decrease mucoadhesion, which may increase the delivery of the mucus penetrating lipid nanoparticles to the mucosal tissue.

In some embodiments, the mucus penetrating lipid nanoparticles may be a hypotonic formulation comprising a mucosal penetration enhancing coating. The formulation may be hypotonice for the epithelium to which it is being delivered. Non-limiting examples of hypotonic formulations may be found in International Patent Publication No. WO2013110028, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, in order to enhance the delivery through the mucosal barrier the RNA (e.g., mRNA) vaccine formulation may comprise or be a hypotonic solution. Hypotonic solutions were found to increase the rate at which mucoinert particles such as, but not limited to, mucus-penetrating particles, were able to reach the vaginal epithelial surface (see e.g., Ensign et al. Biomaterials 2013 34(28): 6922-9, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the RNA (e.g., mRNA) vaccine is formulated as a lipoplex, such as, without limitation, the ATUPLEX™ system, the DACC system, the DBTC system and other siRNA-lipoplex technology from Silence Therapeutics (London, United Kingdom), STEMFECT™ from STEMGENT® (Cambridge, Mass.), and polyethylenimine (PEI) or protamine-based targeted and non-targeted delivery of nucleic acids acids (Aleku et al. Cancer Res. 2008 68:9788-9798; Strumberg et al. Int J Clin Pharmacol Ther 2012 50:76-78; Santel et al., Gene Ther 2006 13:1222-1234; Santel et al., Gene Ther 2006 13:1360-1370; Gutbier et al., Pulm Pharmacol. Ther. 2010 23:334-344; Kaufmann et al. Microvasc Res 2010 80:286-293 Weide et al. J Immunother. 2009 32:498-507; Weide et al. J Immunother. 2008 31:180-188; Pascolo Expert Opin. Biol. Ther. 4:1285-1294; Fotin-Mleczek et al., 2011 J. Immunother. 34:1-15; Song et al., Nature Biotechnol. 2005, 23:709-717; Peer et al., Proc Natl Acad Sci USA. 2007 6; 104:4095-4100; deFougerolles Hum Gene Ther. 2008 19:125-132, the contents of each of which are incorporated herein by reference in their entirety).

In some embodiments, such formulations may also be constructed or compositions altered such that they passively or actively are directed to different cell types in vivo, including but not limited to hepatocytes, immune cells, tumor cells, endothelial cells, antigen presenting cells, and leukocytes (Akinc et al. Mol Ther. 2010 18:1357-1364; Song et al., Nat Biotechnol. 2005 23:709-717; Judge et al., J Clin Invest. 2009 119:661-673; Kaufmann et al., Microvasc Res 2010 80:286-293; Santel et al., Gene Ther 2006 13:1222-1234; Santel et al., Gene Ther 2006 13:1360-1370; Gutbier et al., Pulm Pharmacol. Ther. 2010 23:334-344; Basha et al., Mol. Ther. 2011 19:2186-2200; Fenske and Cullis, Expert Opin Drug Deliv. 2008 5:25-44; Peer et al., Science. 2008 319:627-630; Peer and Lieberman, Gene Ther. 2011 18:1127-1133, the contents of each of which are incorporated herein by reference in their entirety). One example of passive targeting of formulations to liver cells includes the DLin-DMA, DLin-KC2-DMA and DLin-MC3-DMA-based lipid nanoparticle formulations, which have been shown to bind to apolipoprotein E and promote binding and uptake of these formulations into hepatocytes in vivo (Akinc et al. Mol Ther. 2010 18:1357-1364, the contents of which are incorporated herein by reference in their entirety). Formulations can also be selectively targeted through expression of different ligands on their surface as exemplified by, but not limited by, folate, transferrin, N-acetylga-

lactosamine (GalNAc), and antibody targeted approaches (Kolhatkar et al., Curr Drug Discov Technol. 2011 8:197-206; Musacchio and Torchilin, Front Biosci. 2011 16:1388-1412; Yu et al., Mol Membr Biol. 2010 27:286-298; Patil et al., Crit Rev Ther Drug Carrier Syst. 2008 25:1-61; Benoit et al., Biomacromolecules. 2011 12:2708-2714; Zhao et al., Expert Opin Drug Deliv. 2008 5:309-319; Akinc et al., Mol Ther. 2010 18:1357-1364; Srinivasan et al., Methods Mol Biol. 2012 820:105-116; Ben-Arie et al., Methods Mol Biol. 2012 757:497-507; Peer 2010 J Control Release. 20:63-68; Peer et al., Proc Natl Acad Sci USA. 2007 104:4095-4100; Kim et al., Methods Mol Biol. 2011 721:339-353; Subramanya et al., Mol Ther. 2010 18:2028-2037; Song et al., Nat Biotechnol. 2005 23:709-717; Peer et al., Science. 2008 319:627-630; Peer and Lieberman, Gene Ther. 2011 18:1127-1133, the contents of each of which are incorporated herein by reference in their entirety).

In some embodiments, the RNA (e.g., mRNA) vaccine is formulated as a solid lipid nanoparticle. A solid lipid nanoparticle (SLN) may be spherical with an average diameter between 10 to 1000 nm. SLN possess a solid lipid core matrix that can solubilize lipophilic molecules and may be stabilized with surfactants and/or emulsifiers. In some embodiments, the lipid nanoparticle may be a self-assembly lipid-polymer nanoparticle (see Zhang et al., ACS Nano, 2008, 2 (8), pp 1696-1702; the contents of which are herein incorporated by reference in their entirety). As a non-limiting example, the SLN may be the SLN described in International Patent Publication No. WO2013105101, the contents of which are herein incorporated by reference in their entirety. As another non-limiting example, the SLN may be made by the methods or processes described in International Patent Publication No. WO2013105101, the contents of which are herein incorporated by reference in their entirety.

Liposomes, lipoplexes, or lipid nanoparticles may be used to improve the efficacy of polynucleotides directed protein production as these formulations may be able to increase cell transfection by the RNA (e.g., mRNA) vaccine; and/or increase the translation of encoded protein. One such example involves the use of lipid encapsulation to enable the effective systemic delivery of polyplex plasmid DNA (Heyes et al., Mol Ther. 2007 15: 713-720; the contents of which are incorporated herein by reference in their entirety). The liposomes, lipoplexes, or lipid nanoparticles may also be used to increase the stability of the polynucleotide.

In some embodiments, the RNA (e.g., mRNA) vaccines of the present disclosure can be formulated for controlled release and/or targeted delivery. As used herein, "controlled release" refers to a pharmaceutical composition or compound release profile that conforms to a particular pattern of release to effect a therapeutic outcome. In some embodiments, the RNA (e.g., mRNA) vaccines may be encapsulated into a delivery agent described herein and/or known in the art for controlled release and/or targeted delivery. As used herein, the term "encapsulate" means to enclose, surround or encase. As it relates to the formulation of the compounds of the disclosure, encapsulation may be substantial, complete or partial. The term "substantially encapsulated" means that at least greater than 50, 60, 70, 80, 85, 90, 95, 96, 97, 98, 99, 99.9, 99.9 or greater than 99.999% of the pharmaceutical composition or compound of the disclosure may be enclosed, surrounded or encased within the delivery agent. "Partially encapsulation" means that less than 10, 10, 20, 30, 40 50 or less of the pharmaceutical composition or compound of the disclosure may be enclosed, surrounded or encased within the delivery agent. Advantageously, encapsulation may be determined by measuring the escape or the activity of the pharmaceutical composition or compound of the disclosure using fluorescence and/or electron micrograph. For example, at least 1, 5, 10, 20, 30, 40, 50, 60, 70, 80, 85, 90, 95, 96, 97, 98, 99, 99.9, 99.99 or greater than 99.99% of the pharmaceutical composition or compound of the disclosure are encapsulated in the delivery agent.

In some embodiments, the controlled release formulation may include, but is not limited to, tri-block co-polymers. As a non-limiting example, the formulation may include two different types of tri-block co-polymers (International Pub. No. WO2012131104 and

WO2012131106, the contents of each of which are incorporated herein by reference in their entirety).

In some embodiments, the RNA (e.g., mRNA) vaccines may be encapsulated into a lipid nanoparticle or a rapidly eliminated lipid nanoparticle and the lipid nanoparticles or a rapidly eliminated lipid nanoparticle may then be encapsulated into a polymer, hydrogel and/or surgical sealant described herein and/or known in the art. As a non-limiting example, the polymer, hydrogel or surgical sealant may be PLGA, ethylene vinyl acetate (EVAc), poloxamer, GELSITE® (Nanotherapeutics, Inc. Alachua, Fla.), HYLENEX® (Halozyme Therapeutics, San Diego Calif.), surgical sealants such as fibrinogen polymers (Ethicon Inc. Cornelia, Ga.), TISSELL® (Baxter International, Inc Deerfield, Ill.), PEG-based sealants, and COSEAL® (Baxter International, Inc Deerfield, Ill.).

In some embodiments, the lipid nanoparticle may be encapsulated into any polymer known in the art which may form a gel when injected into a subject. As another non-limiting example, the lipid nanoparticle may be encapsulated into a polymer matrix which may be biodegradable.

In some embodiments, the RNA (e.g., mRNA) vaccine formulation for controlled release and/or targeted delivery may also include at least one controlled release coating. Controlled release coatings include, but are not limited to, OPADRY®, polyvinylpyrrolidone/vinyl acetate copolymer, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, EUDRAGIT RL®, EUDRAGIT RS® and cellulose derivatives such as ethylcellulose aqueous dispersions (AQUACOAT® and SURELEASE®).

In some embodiments, the RNA (e.g., mRNA) vaccine controlled release and/or targeted delivery formulation may comprise at least one degradable polyester which may contain polycationic side chains. Degradable polyesters include, but are not limited to, poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester), and combinations thereof. In some embodiments, the degradable polyesters may include a PEG conjugation to form a PEGylated polymer.

In some embodiments, the RNA (e.g., mRNA) vaccine controlled release and/or targeted delivery formulation comprising at least one polynucleotide may comprise at least one PEG and/or PEG related polymer derivatives as described in U.S. Pat. No. 8,404,222, the contents of which are incorporated herein by reference in their entirety.

In some embodiments, the RNA (e.g., mRNA) vaccine controlled release delivery formulation comprising at least one polynucleotide may be the controlled release polymer system described in US20130130348, the contents of which are incorporated herein by reference in their entirety.

In some embodiments, the RNA (e.g., mRNA) vaccines of the present disclosure may be encapsulated in a therapeutic nanoparticle, referred to herein as "therapeutic nanoparticle RNA (e.g., mRNA) vaccines." Therapeutic nanoparticles

may be formulated by methods described herein and known in the art such as, but not limited to, International Pub Nos. WO2010005740, WO2010030763, WO2010005721, WO2010005723, WO2012054923, U.S. Publication Nos. US20110262491, US20100104645, US20100087337, US20100068285, US20110274759, US20100068286, US20120288541, US20130123351 and US20130230567 and U.S. Pat. Nos. 8,206,747, 8,293,276, 8,318,208 and 8,318,211; the contents of each of which are herein incorporated by reference in their entirety. In some embodiments, therapeutic polymer nanoparticles may be identified by the methods described in US Pub No. US20120140790, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the therapeutic nanoparticle RNA (e.g., mRNA) vaccine may be formulated for sustained release. As used herein, "sustained release" refers to a pharmaceutical composition or compound that conforms to a release rate over a specific period of time. The period of time may include, but is not limited to, hours, days, weeks, months and years. As a non-limiting example, the sustained release nanoparticle may comprise a polymer and a therapeutic agent such as, but not limited to, the polynucleotides of the present disclosure (see International Pub No. 2010075072 and US Pub No. US20100216804, US20110217377 and US20120201859, the contents of each of which are incorporated herein by reference in their entirety). In another non-limiting example, the sustained release formulation may comprise agents which permit persistent bioavailability such as, but not limited to, crystals, macromolecular gels and/or particulate suspensions (see U.S. Patent Publication No US20130150295, the contents of each of which are incorporated herein by reference in their entirety).

In some embodiments, the therapeutic nanoparticle RNA (e.g., mRNA) vaccines may be formulated to be target specific. As a non-limiting example, the therapeutic nanoparticles may include a corticosteroid (see International Pub. No. WO2011084518, the contents of which are incorporated herein by reference in their entirety). As a non-limiting example, the therapeutic nanoparticles may be formulated in nanoparticles described in International Pub No. WO2008121949, WO2010005726, WO2010005725, WO2011084521 and US Pub No. US20100069426, US20120004293 and US20100104655, the contents of each of which are incorporated herein by reference in their entirety.

In some embodiments, the nanoparticles of the present disclosure may comprise a polymeric matrix. As a non-limiting example, the nanoparticle may comprise two or more polymers such as, but not limited to, polyethylenes, polycarbonates, polyanhydrides, polyhydroxyacids, polypropylfumerates, polycaprolactones, polyamides, polyacetals, polyethers, polyesters, poly(orthoesters), polycyanoacrylates, polyvinyl alcohols, polyurethanes, polyphosphazenes, polyacrylates, polymethacrylates, polycyanoacrylates, polyureas, polystyrenes, polyamines, polylysine, poly(ethylene imine), poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester) or combinations thereof.

In some embodiments, the therapeutic nanoparticle comprises a diblock copolymer. In some embodiments, the diblock copolymer may include PEG in combination with a polymer such as, but not limited to, polyethylenes, polycarbonates, polyanhydrides, polyhydroxyacids, polypropylfumerates, polycaprolactones, polyamides, polyacetals, polyethers, polyesters, poly(orthoesters), polycyanoacrylates, polyvinyl alcohols, polyurethanes, polyphosphazenes, polyacrylates, polymethacrylates, polycyanoacrylates, polyureas, polystyrenes, polyamines, polylysine, poly(ethylene imine), poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester) or combinations thereof. In yet another embodiment, the diblock copolymer may be a high-X diblock copolymer such as those described in International Patent Publication No. WO2013120052, the contents of which are incorporated herein by reference in their entirety.

As a non-limiting example the therapeutic nanoparticle comprises a PLGA-PEG block copolymer (see U.S. Publication No. US20120004293 and U.S. Pat. No. 8,236,330, each of which is herein incorporated by reference in their entirety). In another non-limiting example, the therapeutic nanoparticle is a stealth nanoparticle comprising a diblock copolymer of PEG and PLA or PEG and PLGA (see U.S. Pat. No. 8,246,968 and International Publication No. WO2012166923, the contents of each of which are herein incorporated by reference in their entirety). In yet another non-limiting example, the therapeutic nanoparticle is a stealth nanoparticle or a target-specific stealth nanoparticle as described in U.S. Patent Publication No. US20130172406, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the therapeutic nanoparticle may comprise a multiblock copolymer (see e.g., U.S. Pat. Nos. 8,263,665 and 8,287,910 and U.S. Patent Pub. No. US20130195987, the contents of each of which are herein incorporated by reference in their entirety).

In yet another non-limiting example, the lipid nanoparticle comprises the block copolymer PEG-PLGA-PEG (see e.g., the thermosensitive hydrogel (PEG-PLGA-PEG) was used as a TGF-beta1 gene delivery vehicle in Lee et al. Thermosensitive Hydrogel as a Tgf-β1 Gene Delivery Vehicle Enhances Diabetic Wound Healing. Pharmaceutical Research, 2003 20(12): 1995-2000; as a controlled gene delivery system in Li et al. Controlled Gene Delivery System Based on Thermosensitive Biodegradable Hydrogel. Pharmaceutical Research 2003 20(6):884-888; and Chang et al., Non-ionic amphiphilic biodegradable PEG-PLGA-PEG copolymer enhances gene delivery efficiency in rat skeletal muscle. J Controlled Release. 2007 118:245-253, the contents of each of which are herein incorporated by reference in their entirety). The RNA (e.g., mRNA) vaccines of the present disclosure may be formulated in lipid nanoparticles comprising the PEG-PLGA-PEG block copolymer.

In some embodiments, the therapeutic nanoparticle may comprise a multiblock copolymer (see e.g., U.S. Pat. Nos. 8,263,665 and 8,287,910 and U.S. Patent Pub. No. US20130195987, the contents of each of which are herein incorporated by reference in their entirety).

In some embodiments, the block copolymers described herein may be included in a polyion complex comprising a non-polymeric micelle and the block copolymer. (see e.g., U.S. Publication No. 20120076836, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the therapeutic nanoparticle may comprise at least one acrylic polymer. Acrylic polymers include but are not limited to, acrylic acid, methacrylic acid, acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, amino alkyl methacrylate copolymer, poly (acrylic acid), poly(methacrylic acid), polycyanoacrylates and combinations thereof.

In some embodiments, the therapeutic nanoparticles may comprise at least one poly(vinyl ester) polymer. The poly

(vinyl ester) polymer may be a copolymer such as a random copolymer. As a non-limiting example, the random copolymer may have a structure such as those described in International Application No. WO2013032829 or U.S. Patent Publication No US20130121954, the contents of each of which are herein incorporated by reference in their entirety. In some embodiments, the poly(vinyl ester) polymers may be conjugated to the polynucleotides described herein.

In some embodiments, the therapeutic nanoparticle may comprise at least one diblock copolymer. The diblock copolymer may be, but it not limited to, a poly(lactic) acid-poly (ethylene)glycol copolymer (see, e.g., International Patent Publication No. WO2013044219, the contents of which are herein incorporated by reference in their entirety). As a non-limiting example, the therapeutic nanoparticle may be used to treat cancer (see International publication No. WO2013044219, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the therapeutic nanoparticles may comprise at least one cationic polymer described herein and/or known in the art.

In some embodiments, the therapeutic nanoparticles may comprise at least one amine-containing polymer such as, but not limited to polylysine, polyethylene imine, poly(amidoamine) dendrimers, poly(beta-amino esters) (see, e.g., U.S. Pat. No. 8,287,849, the contents of which are herein incorporated by reference in their entirety) and combinations thereof.

In some embodiments, the nanoparticles described herein may comprise an amine cationic lipid such as those described in International Patent Application No. WO2013059496, the contents of which are herein incorporated by reference in their entirety. In some embodiments, the cationic lipids may have an amino-amine or an amino-amide moiety.

In some embodiments, the therapeutic nanoparticles may comprise at least one degradable polyester which may contain polycationic side chains. Degradeable polyesters include, but are not limited to, poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester), and combinations thereof. In some embodiments, the degradable polyesters may include a PEG conjugation to form a PEGylated polymer.

In some embodiments, the synthetic nanocarriers may contain an immunostimulatory agent to enhance the immune response from delivery of the synthetic nanocarrier. As a non-limiting example, the synthetic nanocarrier may comprise a Th1 immunostimulatory agent, which may enhance a Th1-based response of the immune system (see International Pub No. WO2010123569 and U.S. Publication No. US20110223201, the contents of each of which are herein incorporated by reference in their entirety).

In some embodiments, the synthetic nanocarriers may be formulated for targeted release. In some embodiments, the synthetic nanocarrier is formulated to release the polynucleotides at a specified pH and/or after a desired time interval. As a non-limiting example, the synthetic nanoparticle may be formulated to release the RNA (e.g., mRNA) vaccines after 24 hours and/or at a pH of 4.5 (see International Publication Nos. WO2010138193 and WO2010138194 and US Pub Nos. US20110020388 and US20110027217, each of which is herein incorporated by reference in their entireties).

In some embodiments, the synthetic nanocarriers may be formulated for controlled and/or sustained release of the polynucleotides described herein. As a non-limiting example, the synthetic nanocarriers for sustained release may be formulated by methods known in the art, described herein and/or as described in International Pub No. WO2010138192 and US Pub No. 20100303850, each of which is herein incorporated by reference in their entirety.

In some embodiments, the RNA (e.g., mRNA) vaccine may be formulated for controlled and/or sustained release wherein the formulation comprises at least one polymer that is a crystalline side chain (CYSC) polymer. CYSC polymers are described in U.S. Pat. No. 8,399,007, herein incorporated by reference in its entirety.

In some embodiments, the synthetic nanocarrier may be formulated for use as a vaccine. In some embodiments, the synthetic nanocarrier may encapsulate at least one polynucleotide which encode at least one antigen. As a non-limiting example, the synthetic nanocarrier may include at least one antigen and an excipient for a vaccine dosage form (see International Publication No. WO2011150264 and U.S. Publication No. US20110293723, the contents of each of which are herein incorporated by reference in their entirety). As another non-limiting example, a vaccine dosage form may include at least two synthetic nanocarriers with the same or different antigens and an excipient (see International Publication No. WO2011150249 and U.S. Publication No. US20110293701, the contents of each of which are herein incorporated by reference in their entirety). The vaccine dosage form may be selected by methods described herein, known in the art and/or described in International Publication No. WO2011150258 and U.S. Publication No. US20120027806, the contents of each of which are herein incorporated by reference in their entirety).

In some embodiments, the synthetic nanocarrier may comprise at least one polynucleotide which encodes at least one adjuvant. As non-limiting example, the adjuvant may comprise dimethyldioctadecylammonium-bromide, dimethyldioctadecylammonium-chloride, dimethyldioctadecylammonium-phosphate or dimethyldioctadecylammonium-acetate (DDA) and an apolar fraction or part of said apolar fraction of a total lipid extract of a *mycobacterium* (see, e.g., U.S. Pat. No. 8,241,610, the content of which is herein incorporated by reference in its entirety). In some embodiments, the synthetic nanocarrier may comprise at least one polynucleotide and an adjuvant. As a non-limiting example, the synthetic nanocarrier comprising and adjuvant may be formulated by the methods described in International Publication No. WO2011150240 and U.S. Publication No. US20110293700, the contents of each of which are herein incorporated by reference in their entirety.

In some embodiments, the synthetic nanocarrier may encapsulate at least one polynucleotide that encodes a peptide, fragment or region from a virus. As a non-limiting example, the synthetic nanocarrier may include, but is not limited to, any of the nanocarriers described in International Publication No. WO2012024621, WO201202629, WO2012024632 and U.S. Publication No. US20120064110, US20120058153 and US20120058154, the contents of each of which are herein incorporated by reference in their entirety.

In some embodiments, the synthetic nanocarrier may be coupled to a polynucleotide which may be able to trigger a humoral and/or cytotoxic T lymphocyte (CTL) response (see, e.g., International Publication No. WO2013019669, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the RNA (e.g., mRNA) vaccine may be encapsulated in, linked to and/or associated with zwitterionic lipids. Non-limiting examples of zwitterionic lipids and methods of using zwitterionic lipids are described in U.S. Patent Publication No. US20130216607, the con-

tents of which are herein incorporated by reference in their entirety. In some aspects, the zwitterionic lipids may be used in the liposomes and lipid nanoparticles described herein.

In some embodiments, the RNA (e.g., mRNA) vaccine may be formulated in colloid nanocarriers as described in U.S. Patent Publication No. US20130197100, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the nanoparticle may be optimized for oral administration. The nanoparticle may comprise at least one cationic biopolymer such as, but not limited to, chitosan or a derivative thereof. As a non-limiting example, the nanoparticle may be formulated by the methods described in U.S. Publication No. 20120282343, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, LNPs comprise the lipid KL52 (an amino-lipid disclosed in U.S. Application Publication No. 2012/0295832, the contents of which are herein incorporated by reference in their entirety. Activity and/or safety (as measured by examining one or more of ALT/AST, white blood cell count and cytokine induction, for example) of LNP administration may be improved by incorporation of such lipids. LNPs comprising KL52 may be administered intravenously and/or in one or more doses. In some embodiments, administration of LNPs comprising KL52 results in equal or improved mRNA and/or protein expression as compared to LNPs comprising MC3.

In some embodiments, RNA (e.g., mRNA) vaccine may be delivered using smaller LNPs. Such particles may comprise a diameter from below 0.1 um up to 100 nm such as, but not limited to, less than 0.1 um, less than 1.0 um, less than 5 um, less than 10 um, less than 15 um, less than 20 um, less than 25 um, less than 30 um, less than 35 um, less than 40 um, less than 50 um, less than 55 um, less than 60 um, less than 65 um, less than 70 um, less than 75 um, less than 80 um, less than 85 um, less than 90 um, less than 95 um, less than 100 um, less than 125 um, less than 150 um, less than 175 um, less than 200 um, less than 225 um, less than 250 um, less than 275 um, less than 300 um, less than 325 um, less than 350 um, less than 375 um, less than 400 um, less than 425 um, less than 450 um, less than 475 um, less than 500 um, less than 525 um, less than 550 um, less than 575 um, less than 600 um, less than 625 um, less than 650 um, less than 675 um, less than 700 um, less than 725 um, less than 750 um, less than 775 um, less than 800 um, less than 825 um, less than 850 um, less than 875 um, less than 900 um, less than 925 um, less than 950 um, less than 975 um, or less than 1000 um.

In some embodiments, RNA (e.g., mRNA) vaccines may be delivered using smaller LNPs, which may comprise a diameter from about 1 nm to about 100 nm, from about 1 nm to about 10 nm, about 1 nm to about 20 nm, from about 1 nm to about 30 nm, from about 1 nm to about 40 nm, from about 1 nm to about 50 nm, from about 1 nm to about 60 nm, from about 1 nm to about 70 nm, from about 1 nm to about 80 nm, from about 1 nm to about 90 nm, from about 5 nm to about from 100 nm, from about 5 nm to about 10 nm, about 5 nm to about 20 nm, from about 5 nm to about 30 nm, from about 5 nm to about 40 nm, from about 5 nm to about 50 nm, from about 5 nm to about 60 nm, from about 5 nm to about 70 nm, from about 5 nm to about 80 nm, from about 5 nm to about 90 nm, about 10 to about 50 nm, from about 20 to about 50 nm, from about 30 to about 50 nm, from about 40 to about 50 nm, from about 20 to about 60 nm, from about 30 to about 60 nm, from about 40 to about 60 nm, from about 20 to about 70 nm, from about 30 to about 70 nm, from about 40 to about 70 nm, from about 50 to about 70 nm, from about 60 to about 70 nm, from about 20 to about 80 nm, from about 30 to about 80 nm, from about 40 to about 80 nm, from about 50 to about 80 nm, from about 60 to about 80 nm, from about 20 to about 90 nm, from about 30 to about 90 nm, from about 40 to about 90 nm, from about 50 to about 90 nm, from about 60 to about 90 nm and/or from about 70 to about 90 nm.

In some embodiments, such LNPs are synthesized using methods comprising microfluidic mixers. Examples of microfluidic mixers may include, but are not limited to, a slit interdigital micromixer including, but not limited to those manufactured by Microinnova (Allerheiligen bei Wildon, Austria) and/or a staggered herringbone micromixer (SHM) (Zhigaltsev, I. V. et al., Bottom-up design and synthesis of limit size lipid nanoparticle systems with aqueous and triglyceride cores using millisecond microfluidic mixing have been published (Langmuir. 2012. 28:3633-40; Belliveau, N. M. et al., Microfluidic synthesis of highly potent limit-size lipid nanoparticles for in vivo delivery of siRNA. Molecular Therapy-Nucleic Acids. 2012. 1:e37; Chen, D. et al., Rapid discovery of potent siRNA-containing lipid nanoparticles enabled by controlled microfluidic formulation. J Am Chem Soc. 2012. 134(16):6948-51, the contents of each of which are herein incorporated by reference in their entirety). In some embodiments, methods of LNP generation comprising SHM, further comprise the mixing of at least two input streams wherein mixing occurs by microstructure-induced chaotic advection (MICA). According to this method, fluid streams flow through channels present in a herringbone pattern causing rotational flow and folding the fluids around each other. This method may also comprise a surface for fluid mixing wherein the surface changes orientations during fluid cycling. Methods of generating LNPs using SHM include those disclosed in U.S. Application Publication Nos. 2004/0262223 and 2012/0276209, the contents of each of which are herein incorporated by reference in their entirety.

In some embodiments, the RNA (e.g., mRNA) vaccine of the present disclosure may be formulated in lipid nanoparticles created using a micromixer such as, but not limited to, a Slit Interdigital Microstructured Mixer (SIMM-V2) or a Standard Slit Interdigital Micro Mixer (SSIMM) or Caterpillar (CPMM) or Impinging-jet (IJMM) from the Institut für Mikrotechnik Mainz GmbH, Mainz Germany).

In some embodiments, the RNA (e.g., mRNA) vaccines of the present disclosure may be formulated in lipid nanoparticles created using microfluidic technology (see, e.g., Whitesides, George M. The Origins and the Future of Microfluidics. Nature, 2006 442: 368-373; and Abraham et al. Chaotic Mixer for Microchannels. Science, 2002 295: 647-651; each of which is herein incorporated by reference in its entirety). As a non-limiting example, controlled microfluidic formulation includes a passive method for mixing streams of steady pressure-driven flows in micro channels at a low Reynolds number (see, e.g., Abraham et al. Chaotic Mixer for Microchannels. Science, 2002 295: 647-651, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the RNA (e.g., mRNA) vaccines of the present disclosure may be formulated in lipid nanoparticles created using a micromixer chip such as, but not limited to, those from Harvard Apparatus (Holliston, Mass.) or Dolomite Microfluidics (Royston, UK). A micromixer chip can be used for rapid mixing of two or more fluid streams with a split and recombine mechanism.

In some embodiments, the RNA (e.g., mRNA) vaccines of the disclosure may be formulated for delivery using the drug

encapsulating microspheres described in International Patent Publication No. WO2013063468 or U.S. Pat. No. 8,440,614, the contents of each of which are herein incorporated by reference in their entirety. The microspheres may comprise a compound of the formula (I), (II), (III), (IV), (V) or (VI) as described in International Patent Publication No. WO2013063468, the contents of which are herein incorporated by reference in their entirety. In some embodiments, the amino acid, peptide, polypeptide, lipids (APPL) are useful in delivering the RNA (e.g., mRNA) vaccines of the disclosure to cells (see International Patent Publication No. WO2013063468, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the RNA (e.g., mRNA) vaccines of the disclosure may be formulated in lipid nanoparticles having a diameter from about 10 to about 100 nm such as, but not limited to, about 10 to about 20 nm, about 10 to about 30 nm, about 10 to about 40 nm, about 10 to about 50 nm, about 10 to about 60 nm, about 10 to about 70 nm, about 10 to about 80 nm, about 10 to about 90 nm, about 20 to about 30 nm, about 20 to about 40 nm, about 20 to about 50 nm, about 20 to about 60 nm, about 20 to about 70 nm, about 20 to about 80 nm, about 20 to about 90 nm, about 20 to about 100 nm, about 30 to about 40 nm, about 30 to about 50 nm, about 30 to about 60 nm, about 30 to about 70 nm, about 30 to about 80 nm, about 30 to about 90 nm, about 30 to about 100 nm, about 40 to about 50 nm, about 40 to about 60 nm, about 40 to about 70 nm, about 40 to about 80 nm, about 40 to about 90 nm, about 40 to about 100 nm, about 50 to about 60 nm, about 50 to about 70 nm about 50 to about 80 nm, about 50 to about 90 nm, about 50 to about 100 nm, about 60 to about 70 nm, about 60 to about 80 nm, about 60 to about 90 nm, about 60 to about 100 nm, about 70 to about 80 nm, about 70 to about 90 nm, about 70 to about 100 nm, about 80 to about 90 nm, about 80 to about 100 nm and/or about 90 to about 100 nm.

In some embodiments, the lipid nanoparticles may have a diameter from about 10 to 500 nm.

In some embodiments, the lipid nanoparticle may have a diameter greater than 100 nm, greater than 150 nm, greater than 200 nm, greater than 250 nm, greater than 300 nm, greater than 350 nm, greater than 400 nm, greater than 450 nm, greater than 500 nm, greater than 550 nm, greater than 600 nm, greater than 650 nm, greater than 700 nm, greater than 750 nm, greater than 800 nm, greater than 850 nm, greater than 900 nm, greater than 950 nm or greater than 1000 nm.

In some embodiments, the lipid nanoparticle may be a limit size lipid nanoparticle described in International Patent Publication No. WO2013059922, the contents of which are herein incorporated by reference in their entirety. The limit size lipid nanoparticle may comprise a lipid bilayer surrounding an aqueous core or a hydrophobic core; where the lipid bilayer may comprise a phospholipid such as, but not limited to, diacylphosphatidylcholine, a diacylphosphatidylethanolamine, a ceramide, a sphingomyelin, a dihydrosphingomyelin, a cephalin, a cerebroside, a C8-C20 fatty acid diacylphophatidylcholine, and 1-palmitoyl-2-oleoyl phosphatidylcholine (POPC). In some embodiments, the limit size lipid nanoparticle may comprise a polyethylene glycol-lipid such as, but not limited to, DLPE-PEG, DMPE-PEG, DPPC-PEG and DSPE-PEG.

In some embodiments, the RNA (e.g., mRNA) vaccines may be delivered, localized and/or concentrated in a specific location using the delivery methods described in International Patent Publication No. WO2013063530, the contents of which are herein incorporated by reference in their entirety. As a non-limiting example, a subject may be administered an empty polymeric particle prior to, simultaneously with or after delivering the RNA (e.g., mRNA) vaccines to the subject. The empty polymeric particle undergoes a change in volume once in contact with the subject and becomes lodged, embedded, immobilized or entrapped at a specific location in the subject.

In some embodiments, the RNA (e.g., mRNA) vaccines may be formulated in an active substance release system (see, e.g., U.S. Patent Publication No. US20130102545, the contents of which are herein incorporated by reference in their entirety). The active substance release system may comprise 1) at least one nanoparticle bonded to an oligonucleotide inhibitor strand which is hybridized with a catalytically active nucleic acid and 2) a compound bonded to at least one substrate molecule bonded to a therapeutically active substance (e.g., polynucleotides described herein), where the therapeutically active substance is released by the cleavage of the substrate molecule by the catalytically active nucleic acid.

In some embodiments, the RNA (e.g., mRNA) vaccines may be formulated in a nanoparticle comprising an inner core comprising a non-cellular material and an outer surface comprising a cellular membrane. The cellular membrane may be derived from a cell or a membrane derived from a virus. As a non-limiting example, the nanoparticle may be made by the methods described in International Patent Publication No. WO2013052167, the contents of which are herein incorporated by reference in their entirety. As another non-limiting example, the nanoparticle described in International Patent Publication No. WO2013052167, the contents of which are herein incorporated by reference in their entirety, may be used to deliver the RNA (e.g., mRNA) vaccines described herein.

In some embodiments, the RNA (e.g., mRNA) vaccines may be formulated in porous nanoparticle-supported lipid bilayers (protocells). Protocells are described in International Patent Publication No. WO2013056132, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the RNA (e.g., mRNA) vaccines described herein may be formulated in polymeric nanoparticles as described in or made by the methods described in U.S. Pat. Nos. 8,420,123 and 8,518,963 and European Patent No. EP2073848B1, the contents of each of which are herein incorporated by reference in their entirety. As a non-limiting example, the polymeric nanoparticle may have a high glass transition temperature such as the nanoparticles described in or nanoparticles made by the methods described in U.S. Pat. No. 8,518,963, the contents of which are herein incorporated by reference in their entirety. As another non-limiting example, the polymer nanoparticle for oral and parenteral formulations may be made by the methods described in European Patent No. EP2073848B1, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the RNA (e.g., mRNA) vaccines described herein may be formulated in nanoparticles used in imaging. The nanoparticles may be liposome nanoparticles such as those described in U.S. Patent Publication No US20130129636, herein incorporated by reference in its entirety. As a non-limiting example, the liposome may comprise gadolinium(III)2-{4,7-bis-carboxymethyl-10-[(N,N-distearylamidomethyl-N'-amido-methyl]-1,4,7,10-tetra-azacyclododec-1-yl}-acetic acid and a neutral, fully saturated phospholipid component (see, e.g., U.S. Patent Publication No US20130129636, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the nanoparticles which may be used in the present disclosure are formed by the methods described in U.S. Patent Application No. US20130130348, the contents of which are herein incorporated by reference in their entirety.

The nanoparticles of the present disclosure may further include nutrients such as, but not limited to, those which deficiencies can lead to health hazards from anemia to neural tube defects (see, e.g., the nanoparticles described in International Patent Publication No WO2013072929, the contents of which are herein incorporated by reference in their entirety). As a non-limiting example, the nutrient may be iron in the form of ferrous, ferric salts or elemental iron, iodine, folic acid, vitamins or micronutrients.

In some embodiments, the RNA (e.g., mRNA) vaccines of the present disclosure may be formulated in a swellable nanoparticle. The swellable nanoparticle may be, but is not limited to, those described in U.S. Pat. No. 8,440,231, the contents of which are herein incorporated by reference in their entirety. As a non-limiting embodiment, the swellable nanoparticle may be used for delivery of the RNA (e.g., mRNA) vaccines of the present disclosure to the pulmonary system (see, e.g., U.S. Pat. No. 8,440,231, the contents of which are herein incorporated by reference in their entirety).

The RNA (e.g., mRNA) vaccines of the present disclosure may be formulated in polyanhydride nanoparticles such as, but not limited to, those described in U.S. Pat. No. 8,449,916, the contents of which are herein incorporated by reference in their entirety.

The nanoparticles and microparticles of the present disclosure may be geometrically engineered to modulate macrophage and/or the immune response. In some embodiments, the geometrically engineered particles may have varied shapes, sizes and/or surface charges in order to incorporated the polynucleotides of the present disclosure for targeted delivery such as, but not limited to, pulmonary delivery (see, e.g., International Publication No WO2013082111, the contents of which are herein incorporated by reference in their entirety). Other physical features the geometrically engineering particles may have include, but are not limited to, fenestrations, angled arms, asymmetry and surface roughness, charge which can alter the interactions with cells and tissues. As a non-limiting example, nanoparticles of the present disclosure may be made by the methods described in International Publication No WO2013082111, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the nanoparticles of the present disclosure may be water soluble nanoparticles such as, but not limited to, those described in International Publication No. WO2013090601, the contents of which are herein incorporated by reference in their entirety. The nanoparticles may be inorganic nanoparticles which have a compact and zwitterionic ligand in order to exhibit good water solubility. The nanoparticles may also have small hydrodynamic diameters (HD), stability with respect to time, pH, and salinity and a low level of non-specific protein binding.

In some embodiments the nanoparticles of the present disclosure may be developed by the methods described in U.S. Patent Publication No. US20130172406, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the nanoparticles of the present disclosure are stealth nanoparticles or target-specific stealth nanoparticles such as, but not limited to, those described in U.S. Patent Publication No. US20130172406, the contents of which are herein incorporated by reference in their entirety. The nanoparticles of the present disclosure may be made by the methods described in U.S. Patent Publication No. US20130172406, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the stealth or target-specific stealth nanoparticles may comprise a polymeric matrix. The polymeric matrix may comprise two or more polymers such as, but not limited to, polyethylenes, polycarbonates, polyanhydrides, polyhydroxyacids, polypropylfumerates, polycaprolactones, polyamides, polyacetals, polyethers, polyesters, poly(orthoesters), polycyanoacrylates, polyvinyl alcohols, polyurethanes, polyphosphazenes, polyacrylates, polymethacrylates, polycyanoacrylates, polyureas, polystyrenes, polyamines, polyesters, polyanhydrides, polyethers, polyurethanes, polymethacrylates, polyacrylates, polycyanoacrylates or combinations thereof.

In some embodiments, the nanoparticle may be a nanoparticle-nucleic acid hybrid structure having a high density nucleic acid layer. As a non-limiting example, the nanoparticle-nucleic acid hybrid structure may made by the methods described in U.S. Patent Publication No. US20130171646, the contents of which are herein incorporated by reference in their entirety. The nanoparticle may comprise a nucleic acid such as, but not limited to, polynucleotides described herein and/or known in the art.

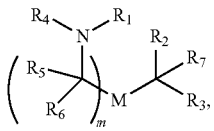
At least one of the nanoparticles of the present disclosure may be embedded in in the core a nanostructure or coated with a low density porous 3-D structure or coating which is capable of carrying or associating with at least one payload within or on the surface of the nanostructure. Non-limiting examples of the nanostructures comprising at least one nanoparticle are described in International Patent Publication No. WO2013123523, the contents of which are herein incorporated by reference in their entirety.

In some embodiments the RNA (e.g., mRNA) vaccine may be associated with a cationic or polycationic compounds, including protamine, nucleoline, spermine or spermidine, or other cationic peptides or proteins, such as poly-L-lysine (PLL), polyarginine, basic polypeptides, cell penetrating peptides (CPPs), including HIV-binding peptides, HIV-1 Tat (HIV), Tat-derived peptides, Penetratin, VP^{22} derived or analog peptides, Pestivirus Ems, HSV, VP^{22} (Herpes simplex), MAP, KALA or protein transduction domains (PTDs), PpT620, prolin-rich peptides, arginine-rich peptides, lysine-rich peptides, MPG-peptide(s), Pep-1, L-oligomers, Calcitonin peptide(s), Antennapedia-derived peptides (particularly from *Drosophila* antennapedia), pAntp, plsl, FGF, Lactoferrin, Transportan, Buforin-2, Bac715-24, SynB, SynB(1), pVEC, hCT-derived peptides, SAP, histones, cationic polysaccharides, for example chitosan, polybrene, cationic polymers, e.g. polyethyleneimine (PEI), cationic lipids, e.g. DOTMA: [1-(2,3-sioleyloxy) propyl)]-N,N,N-trimethylammonium chloride, DMRIE, di-C14-amidine, DOTIM, SAINT, DC-Chol, BGTC, CTAP, DOPC, DODAP, DOPE: Dioleyl phosphatidylethanolamine, DOSPA, DODAB, DOIC, DMEPC, DOGS: Dioctadecylamidoglicylspermin, DIMRI: Dimyristooxypropyl dimethyl hydroxyethyl ammonium bromide, DOTAP: dioleoyloxy-3-(trimethylammonio)propane, DC-6-14: O,O-ditetradecanoyl-N-.alpha.-trimethylammonioacetyl)diethanolamine chloride, CLIP 1: rac-[(2,3-dioctadecyloxypropyl) (2-hydroxyethyl)]-dimethylammonium chloride, CLIP6: rac-[2(2,3-dihexadecyloxypropyloxymethyloxy)ethyl]-trimethylammonium, CLIP9: rac-[2(2,3-dihexadecyloxypropyloxysuccinyloxy)ethyl]-trimethylammonium, oligofectamine, or cationic or polycationic polymers, e.g. modified polyaminoacids, such as beta-aminoacid-polymers

or reversed polyamides, etc., modified polyethylenes, such as PVP (poly(N-ethyl-4-vinylpyridinium bromide)), etc., modified acrylates, such as pDMAEMA (poly(dimethylaminoethyl methylacrylate)), etc., modified amidoamines such as pAMAM (poly(amidoamine)), etc., modified polybetaminoester (PBAE), such as diamine end modified 1,4 butanediol diacrylate-co-5-amino-1-pentanol polymers, etc., dendrimers, such as polypropylamine dendrimers or pAMAM based dendrimers, etc., polyimine(s), such as PEI: poly(ethyleneimine), poly(propyleneimine), etc., polyallylamine, sugar backbone based polymers, such as cyclodextrin based polymers, dextran based polymers, chitosan, etc., silan backbone based polymers, such as PMOXA-PDMS copolymers, etc., blockpolymers consisting of a combination of one or more cationic blocks (e.g. selected from a cationic polymer as mentioned above) and of one or more hydrophilic or hydrophobic blocks (e.g. polyethyleneglycole), etc.

In other embodiments the RNA (e.g., mRNA) vaccine is not associated with a cationic or polycationic compounds.

In some embodiments, a nanoparticle comprises compounds of Formula (I):



(I)

or a salt or isomer thereof, wherein:

R_1 is selected from the group consisting of C_{5-30} alkyl, C_{5-20} alkenyl, —R*YR", —YR", and —R"M'R';

R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, C_{2-14} alkenyl, —R*YR", —YR", and —R*OR", or R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle;

R_4 is selected from the group consisting of a C_{3-6} carbocycle, $—(CH_2)_nQ$, $—(CH_2)_nCHQR$, —CHQR, $—CQ(R)_2$, and unsubstituted C_{1-6} alkyl, where Q is selected from a carbocycle, heterocycle, —OR, $—O(CH_2)_nN(R)_2$, —C(O)OR, —OC(O)R, $—CX_3$, $—CX_2H$, $—CXH_2$, —CN, $—N(R)_2$, $—C(O)N(R)_2$, —N(R)C(O)R, $—N(R)S(O)_2R$, $—N(R)C(O)N(R)_2$, $—N(R)C(S)N(R)_2$, $—N(R)R_8$, $—O(CH_2)_nOR$, $—N(R)C(=NR_9)N(R)_2$, $—N(R)C(=CHR_9)N(R)_2$, $—OC(O)N(R)_2$, —N(R)C(O)OR, —N(OR)C(O)R, —N(OR)S(O)$_2$ R, —N(OR)C(O)OR, $—N(OR)C(O)N(R)_2$, $—N(OR)C(S)N(R)_2$, $—N(OR)C(=NR_9)N(R)_2$, $—N(OR)C(=CHR_9)N(R)_2$, $—C(=NR_9)N(R)_2$, $—C(=NR_9)R$, —C(O)N(R)O R, and $C(R)N(R)_2C(O)OR$, and each n is independently selected from 1, 2, 3, 4, and 5;

each R_5 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R_6 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

M and M' are independently selected from —C(O)O—, —OC(O)—, —C(O)N(R')—, —N(R')C(O)—, —C(O)—, —C(S)—, —C(S)S—, —SC(S)—, —CH(OH)—, —P(O)(OR')O—, $—S(O)_2—$, —S—S—, an aryl group, and a heteroaryl group;

R_7 is selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

R_8 is selected from the group consisting of C_{3-6} carbocycle and heterocycle;

R_9 is selected from the group consisting of H, CN, NO_2, C_{1-6} alkyl, —OR, $—S(O)_2R$, $—S(O)_2N(R)_2$, C_{2-6} alkenyl, C_{3-6} carbocycle and heterocycle;

each R is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R' is independently selected from the group consisting of C_{1-18} alkyl, C_{2-18} alkenyl, —R*YR", —YR", and H;

each R" is independently selected from the group consisting of C_{3-14} alkyl and C_{3-14} alkenyl;

each R* is independently selected from the group consisting of C_{1-12} alkyl and C_{2-12} alkenyl;

each Y is independently a C_{3-6} carbocycle;

each X is independently selected from the group consisting of F, Cl, Br, and I; and

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13.

In some embodiments, a subset of compounds of Formula (I) includes those in which when R_4 is $—(CH_2)_nQ$, $—(CH_2)_nCHQR$, —CHQR, or $—CQ(R)_2$, then (i) Q is not $—N(R)_2$ when n is 1, 2, 3, 4 or 5, or (ii) Q is not 5, 6, or 7-membered heterocycloalkyl when n is 1 or 2.

In some embodiments, another subset of compounds of Formula (I) includes those in which

R_1 is selected from the group consisting of C_{5-30} alkyl, C_{5-20} alkenyl, —R*YR", —YR", and —R"M'R';

R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, C_{2-14} alkenyl, —R*YR", —YR", and —R*OR", or R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle;

R_4 is selected from the group consisting of a C_{3-6} carbocycle, $—(CH_2)_nQ$, $—(CH_2)_nCHQR$, —CHQR, $—CQ(R)_2$, and unsubstituted C_{1-6} alkyl, where Q is selected from a C_{3-6} carbocycle, a 5- to 14-membered heteroaryl having one or more heteroatoms selected from N, O, and S, —OR, $—O(CH_2)_nN(R)_2$, —C(O)OR, —OC(O)R, $—CX_3$, $—CX_2H$, $—CXH_2$, —CN, $—C(O)N(R)_2$, —N(R)C(O)R, $—N(R)S(O)_2R$, $—N(R)C(O)N(R)_2$, $—N(R)C(S)N(R)_2$, $—CRN(R)_2C(O)OR$, $—N(R)R_8$, $—O(CH_2)_nOR$, $—N(R)C(=NR_9)N(R)_2$, $—N(R)C(=CHR_9)N(R)_2$, $—OC(O)N(R)_2$, —N(R)C(O)OR, —N(OR)C(O)R, —N(OR)S(O)$_2$R, —N(OR)C(O)OR, $—N(OR)C(O)N(R)_2$, $—N(OR)C(S)N(R)_2$, $—N(OR)C(=NR_9)N(R)_2$, $—N(OR)C(=CHR_9)N(R)_2$, $—C(=NR_9)N(R)_2$, $—C(=NR_9)R$, —C(O)N(R)O R, and a 5- to 14-membered heterocycloalkyl having one or more heteroatoms selected from N, O, and S which is substituted with one or more substituents selected from oxo (=O), OH, amino, mono- or di-alkylamino, and C_{1-3} alkyl, and each n is independently selected from 1, 2, 3, 4, and 5;

each R_5 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R_6 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

M and M' are independently selected from —C(O)O—, —OC(O)—, —C(O)N(R')—, —N(R')C(O)—, —C(O)—, —C(S)—, —C(S)S—, —SC(S)—, —CH(OH)—, —P(O)(OR')O—, $—S(O)_2—$, —S—S—, an aryl group, and a heteroaryl group;

R_7 is selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

R_8 is selected from the group consisting of C_{3-6} carbocycle and heterocycle;

R_9 is selected from the group consisting of H, CN, NO_2, C_{1-6} alkyl, —OR, $—S(O)_2R$, $—S(O)_2N(R)_2$, C_{2-6} alkenyl, C_{3-6} carbocycle and heterocycle;

each R is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R' is independently selected from the group consisting of C_{1-18} alkyl, C_{2-18} alkenyl, —R*YR", —YR", and H;

each R" is independently selected from the group consisting of C_{3-14} alkyl and C_{3-14} alkenyl;

each R* is independently selected from the group consisting of C_{1-12} alkyl and C_{2-12} alkenyl;

each Y is independently a C_{3-6} carbocycle;

each X is independently selected from the group consisting of F, Cl, Br, and I; and

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13,

or salts or isomers thereof.

In some embodiments, another subset of compounds of Formula (I) includes those in which

R_1 is selected from the group consisting of C_{5-30} alkyl, C_{5-20} alkenyl, —R*YR", —YR", and —R"M'R';

R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, C_{2-14} alkenyl, —R*YR", —YR", and —R*OR", or R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle;

R_4 is selected from the group consisting of a C_{3-6} carbocycle, $—(CH_2)_nQ$, $—(CH_2)_nCHQR$, —CHQR, $—CQ(R)_2$, and unsubstituted C_{1-6} alkyl, where Q is selected from a C_{3-6} carbocycle, a 5- to 14-membered heterocycle having one or more heteroatoms selected from N, O, and S, —OR, $—O(CH_2)_nN(R)_2$, —C(O)OR, —OC(O)R, $—CX_3$, $—CX_2H$, $—CXH_2$, —CN, $—C(O)N(R)_2$, $—N(R)C(O)R$, $—N(R)S(O)_2R$, $—N(R)C(O)N(R)_2$, $—N(R)C(S)N(R)_2$, $—CRN(R)_2C(O)OR$, $—N(R)R_8$, $—O(CH_2)_nOR$, $—N(R)C(=NR_9)N(R)_2$, $—N(R)C(=CHR_9)N(R)_2$, $—OC(O)N(R)_2$, —N(R)C(O)OR, —N(OR)C(O)R, $—N(OR)S(O)_2R$, —N(OR)C(O)OR, $—N(OR)C(O)N(R)_2$, $—N(OR)C(S)N(R)_2$, $—N(OR)C(=NR_9)N(R)_2$, $—N(OR)C(=CHR_9)N(R)_2$, $—C(=NR_9)R$, —C(O)N(R)OR, and $—C(=NR_9)N(R)_2$, and each n is independently selected from 1, 2, 3, 4, and 5; and when Q is a 5- to 14-membered heterocycle and (i) R_4 is $—(CH_2)_nQ$ in which n is 1 or 2, or (ii) R_4 is $—(CH_2)_nCHQR$ in which n is 1, or (iii) R_4 is —CHQR, and $—CQ(R)_2$, then Q is either a 5- to 14-membered heteroaryl or 8- to 14-membered heterocycloalkyl;

each R_5 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R_6 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

M and M' are independently selected from —C(O)O—, —OC(O)—, —C(O)N(R')—, —N(R')C(O)—, —C(O)—, —C(S)—, —C(S)S—, —SC(S)—, —CH(OH)—, —P(O)(OR')O—, $—S(O)_2—$, —S—S—, an aryl group, and a heteroaryl group;

R_7 is selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

R_8 is selected from the group consisting of C_{3-6} carbocycle and heterocycle;

R_9 is selected from the group consisting of H, CN, NO_2, C_{1-6} alkyl, —OR, $—S(O)_2R$, $—S(O)_2N(R)_2$, C_{2-6} alkenyl, C_{3-6} carbocycle and heterocycle;

each R is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R' is independently selected from the group consisting of C_{1-18} alkyl, C_{2-18} alkenyl, —R*YR", —YR", and H;

each R" is independently selected from the group consisting of C_{3-14} alkyl and C_{3-14} alkenyl;

each R* is independently selected from the group consisting of C_{1-12} alkyl and C_{2-12} alkenyl;

each Y is independently a C_{3-6} carbocycle;

each X is independently selected from the group consisting of F, Cl, Br, and I; and

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13,

or salts or isomers thereof.

In some embodiments, another subset of compounds of Formula (I) includes those in which

R_1 is selected from the group consisting of C_{5-30} alkyl, C_{5-20} alkenyl, —R*YR", —YR", and —R"M'R';

R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, C_{2-14} alkenyl, —R*YR", —YR", and —R*OR", or R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle;

R_4 is selected from the group consisting of a C_{3-6} carbocycle, $—(CH_2)_nQ$, $—(CH_2)_nCHQR$, —CHQR, $—CQ(R)_2$, and unsubstituted C_{1-6} alkyl, where Q is selected from a C_{3-6} carbocycle, a 5- to 14-membered heteroaryl having one or more heteroatoms selected from N, O, and S, —OR, $—O(CH_2)_nN(R)_2$, —C(O)OR, —OC(O)R, $—CX_3$, $—CX_2H$, $—CXH_2$, —CN, $—C(O)N(R)_2$, $—N(R)C(O)R$, $—N(R)S(O)_2R$, $—N(R)C(O)N(R)_2$, $—N(R)C(S)N(R)_2$, $—CRN(R)_2C(O)OR$, $—N(R)R_8$, $—O(CH_2)_nOR$, $—N(R)C(=NR_9)N(R)_2$, $—N(R)C(=CHR_9)N(R)_2$, $—OC(O)N(R)_2$, —N(R)C(O)OR, —N(OR)C(O)R, $—N(OR)S(O)_2R$, —N(OR)C(O)OR, $—N(OR)C(O)N(R)_2$, $—N(OR)C(S)N(R)_2$, $—N(OR)C(=NR_9)N(R)_2$, $—N(OR)C(=CHR_9)N(R)_2$, $—C(=NR_9)R$, —C(O)N(R)OR, and $—C(=NR_9)N(R)_2$, and each n is independently selected from 1, 2, 3, 4, and 5;

each R_5 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R_6 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

M and M' are independently selected from —C(O)O—, —OC(O)—, —C(O)N(R')—, —N(R')C(O)—, —C(O)—, —C(S)—, —C(S)S—, —SC(S)—, —CH(OH)—, —P(O)(OR')O—, $—S(O)_2—$, —S—S—, an aryl group, and a heteroaryl group;

R_7 is selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

R_8 is selected from the group consisting of C_{3-6} carbocycle and heterocycle;

R_9 is selected from the group consisting of H, CN, NO_2, C_{1-6} alkyl, —OR, $—S(O)_2R$, $—S(O)_2N(R)_2$, C_{2-6} alkenyl, C_{3-6} carbocycle and heterocycle;

each R is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R' is independently selected from the group consisting of C_{1-18} alkyl, C_{2-18} alkenyl, —R*YR", —YR", and H;

each R" is independently selected from the group consisting of C_{3-14} alkyl and C_{3-14} alkenyl;

each R* is independently selected from the group consisting of C_{1-12} alkyl and C_{2-12} alkenyl;

each Y is independently a C_{3-6} carbocycle;

each X is independently selected from the group consisting of F, Cl, Br, and I; and

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13,

or salts or isomers thereof.

In some embodiments, another subset of compounds of Formula (I) includes those in which

R_1 is selected from the group consisting of C_{5-30} alkyl, C_{5-20} alkenyl, —R*YR", —YR", and —R"M'R';

R_2 and R_3 are independently selected from the group consisting of H, C_{2-14} alkyl, C_{2-14} alkenyl, —R*YR", —YR", and —R*OR", or R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle;

R_4 is $—(CH_2)_nQ$ or $—(CH_2)_nCHQR$, where Q is $—N(R)_2$, and n is selected from 3, 4, and 5;

each R_5 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R_6 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

M and M' are independently selected from —C(O)O—, —OC(O)—, —C(O)N(R')—, —N(R')C(O)—, —C(O)—, —C(S)—, —C(S)S—, —SC(S)—, —CH(OH)—, —P(O)(OR')O—, —S(O)$_2$—, —S—S—, an aryl group, and a heteroaryl group;

R_7 is selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R' is independently selected from the group consisting of C_{1-18} alkyl, C_{2-18} alkenyl, —R*YR", —YR", and H;

each R" is independently selected from the group consisting of C_{3-14} alkyl and C_{3-14} alkenyl;

each R* is independently selected from the group consisting of C_{1-12} alkyl and C_{1-12} alkenyl;

each Y is independently a C_{3-6} carbocycle;

each X is independently selected from the group consisting of F, Cl, Br, and I; and

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13,

or salts or isomers thereof.

In some embodiments, another subset of compounds of Formula (I) includes those in which

R_1 is selected from the group consisting of C_{5-30} alkyl, C_5-20 alkenyl, —R*YR", —YR", and —R"M'R';

R_2 and R_3 are independently selected from the group consisting of C_{1-14} alkyl, C_{2-14} alkenyl, —R*YR", —YR", and —R*OR", or R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle;

R_4 is selected from the group consisting of —$(CH_2)_nQ$, —$(CH_2)_n$CHQR, —CHQR, and —CQ$(R)_2$, where Q is —N$(R)_2$, and n is selected from 1, 2, 3, 4, and 5;

each R_5 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R_6 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

M and M' are independently selected from —C(O)O—, —OC(O)—, —C(O)N(R')—, —N(R')C(O)—, —C(O)—, —C(S)—, —C(S)S—, —SC(S)—, —CH(OH)—, —P(O)(OR')O—, —S(O)$_2$—, —S—S—, an aryl group, and a heteroaryl group;

R_7 is selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R' is independently selected from the group consisting of C_{1-18} alkyl, C_{2-18} alkenyl, —R*YR", —YR", and H;

each R" is independently selected from the group consisting of C_{3-14} alkyl and C_{3-14} alkenyl;

each R* is independently selected from the group consisting of C_{1-12} alkyl and C_{1-12} alkenyl;

each Y is independently a C_{3-6} carbocycle;

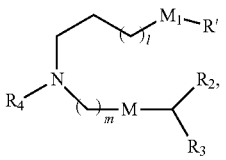
each X is independently selected from the group consisting of F, Cl, Br, and I; and

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13,

or salts or isomers thereof.

In some embodiments, a subset of compounds of Formula (I) includes those of Formula (IA):

(IA)

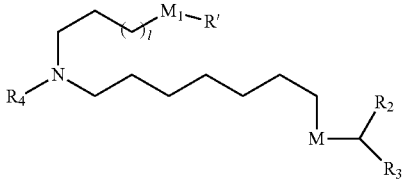


or a salt or isomer thereof, wherein 1 is selected from 1, 2, 3, 4, and 5; m is selected from 5, 6, 7, 8, and 9; M_1 is a bond or M'; R_4 is unsubstituted C_{1-3} alkyl, or —$(CH_2)_nQ$, in which Q is OH, —NHC(S)N$(R)_2$, —NHC(O)N$(R)_2$, —N(R)C(O)R, —N(R)S(O)$_2$R, —N(R)R_8, —NHC(=NR_9)N$(R)_2$, —NHC(=CHR_9)N$(R)_2$, —OC(O)N$(R)_2$, —N(R)C(O)OR, heteroaryl or heterocycloalkyl; M and M' are independently selected

from —C(O)O—, —OC(O)—, —C(O)N(R')—, —P(O)(OR')O—, —S—S—, an aryl group, and a heteroaryl group; and R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, and C_{2-14} alkenyl.

In some embodiments, a subset of compounds of Formula (I) includes those of Formula (II):

(II)

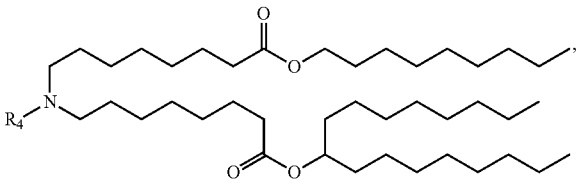


or a salt or isomer thereof, wherein 1 is selected from 1, 2, 3, 4, and 5; M_1 is a bond or M'; R_4 is unsubstituted C_{1-3} alkyl, or —$(CH_2)_nQ$, in which n is 2, 3, or 4, and Q is OH, —NHC(S)N$(R)_2$, —NHC(O)N$(R)_2$, —N(R)C(O)R, —N(R)S(O)$_2$R, —N(R)R_8, —NHC(=NR_9)N$(R)_2$, —NHC(=CHR_9)N$(R)_2$, —OC(O)N$(R)_2$, —N(R)C(O)OR, heteroaryl or heterocycloalkyl; M and M' are independently selected

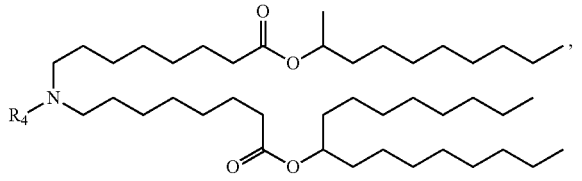
from —C(O)O—, —OC(O)—, —C(O)N(R')—, —P(O)(OR')O—, —S—S—, an aryl group, and a heteroaryl group; and R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, and C_{2-14} alkenyl.

In some embodiments, a subset of compounds of Formula (I) includes those of Formula (IIa), (IIb), (IIc), or (IIe):

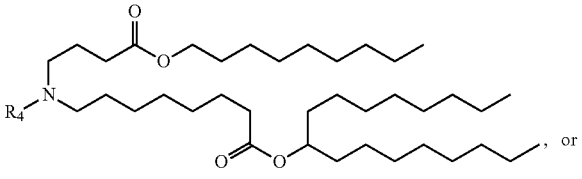
(IIa)



(IIb)



(IIc)



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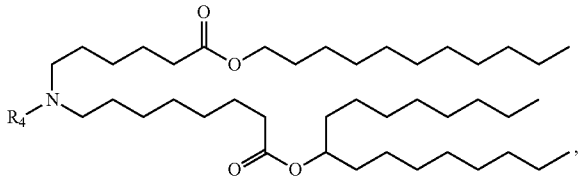
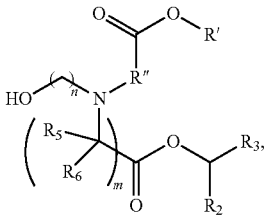
(IIe)



or a salt or isomer thereof, wherein R_4 is as described herein.

In some embodiments, a subset of compounds of Formula (I) includes those of Formula (IId):

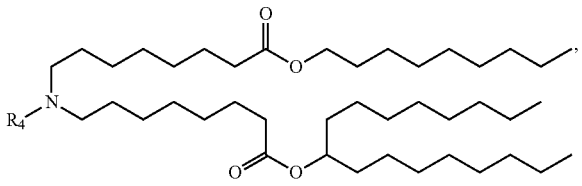
(IId)



or a salt or isomer thereof, wherein n is 2, 3, or 4; and m, R', R", and R_2 through R_6 are as described herein. For example, each of R_2 and R_3 may be independently selected from the group consisting of C_{5-14} alkyl and C_{5-14} alkenyl.

In some embodiments, a subset of compounds of Formula (I) includes those of Formula (IIa), (IIb), (IIc), or (IIe):

(IIa)



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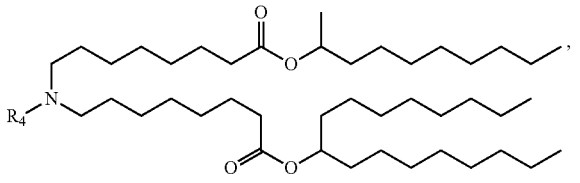
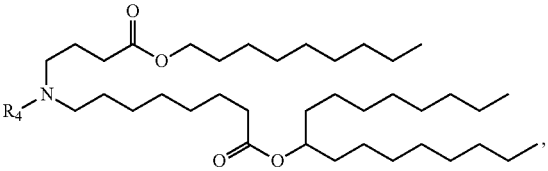
(IIb)

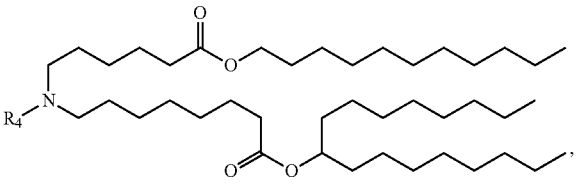


(IIc)



or

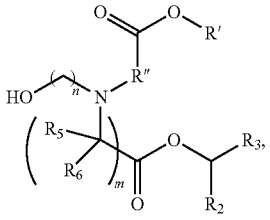
(IIe)



or a salt or isomer thereof, wherein R_4 is as described herein.

In some embodiments, a subset of compounds of Formula (I) includes those of Formula (IId):

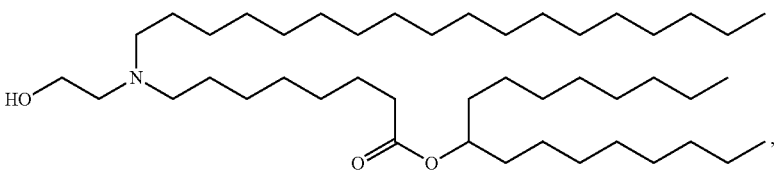
(IId)



or a salt or isomer thereof, wherein n is 2, 3, or 4; and m, R', R", and R_2 through R_6 are as described herein. For example, each of R_2 and R_3 may be independently selected from the group consisting of C_{5-14} alkyl and C_{5-14} alkenyl.

In some embodiments, the compound of Formula (I) is selected from the group consisting of:

(Compound 1)



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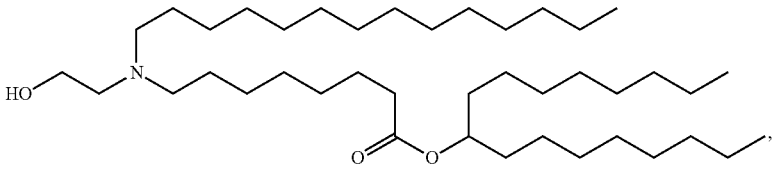
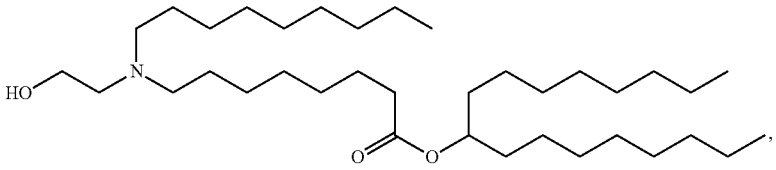
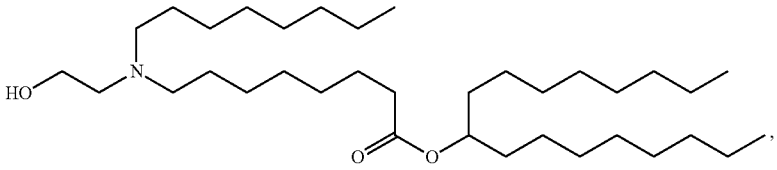
(Compound 2)



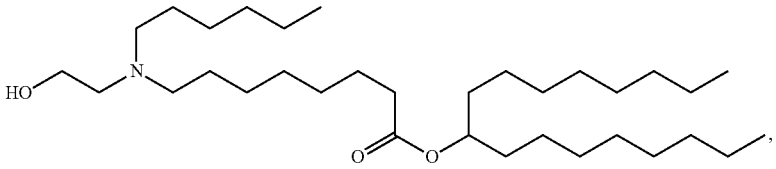
(Compound 3)



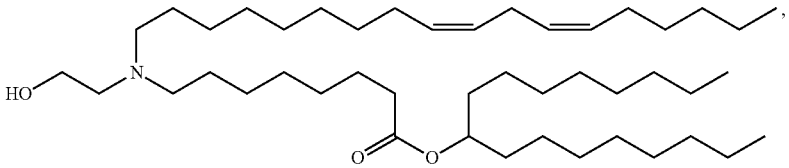
(Compound 4)



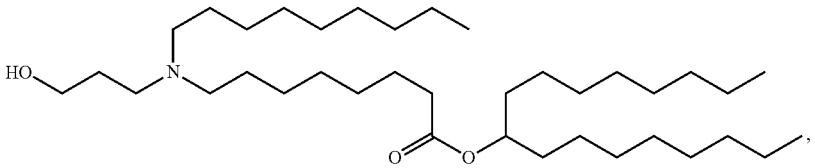
(Compound 5)



(Compound 6)



(Compound 7)



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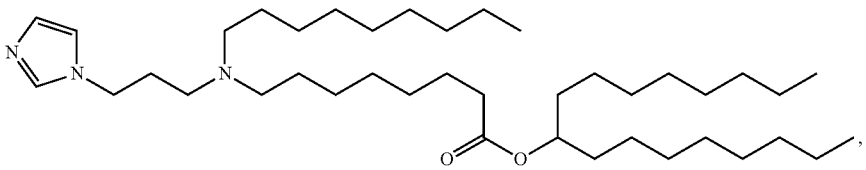

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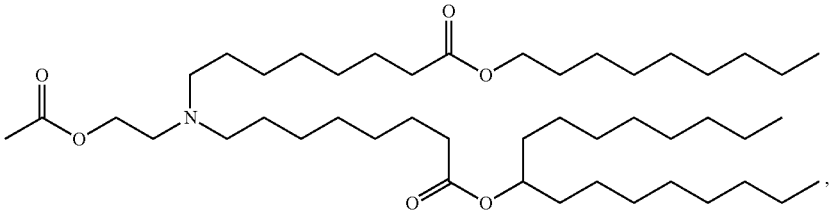

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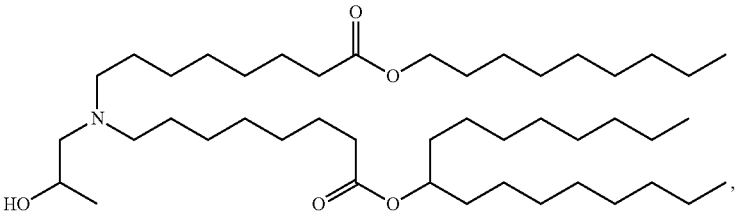

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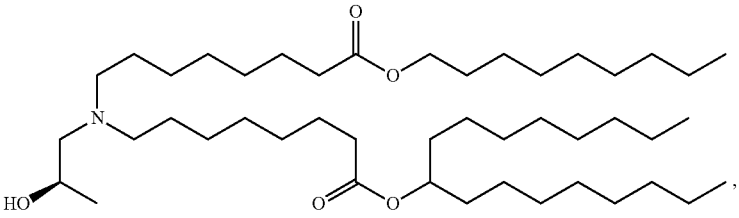

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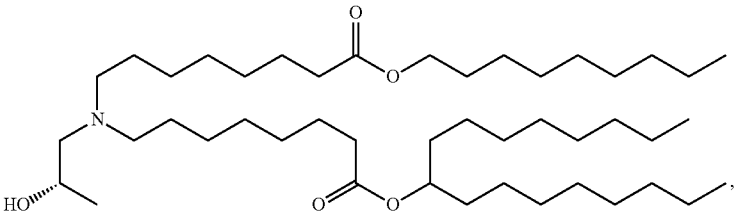

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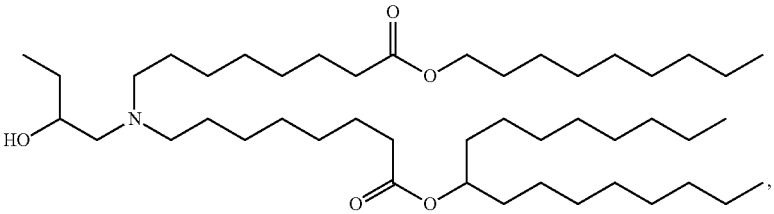

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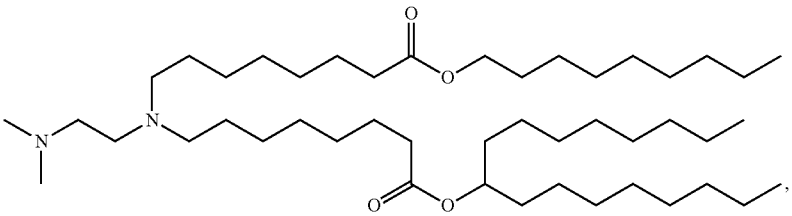

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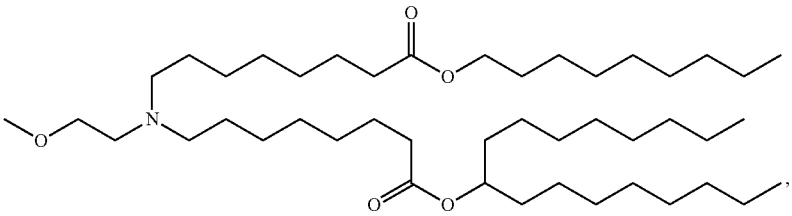

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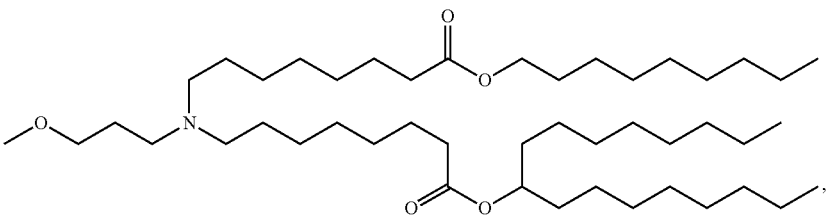

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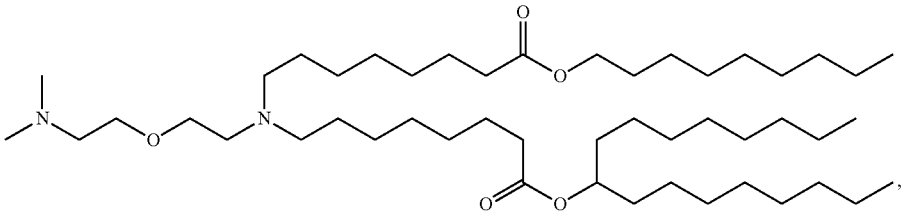

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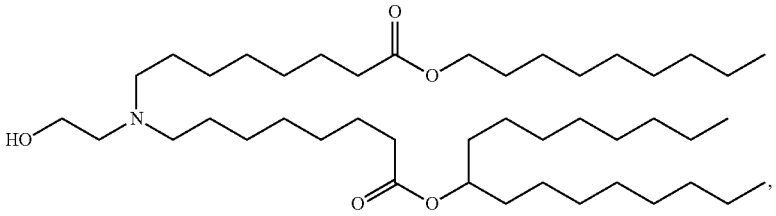

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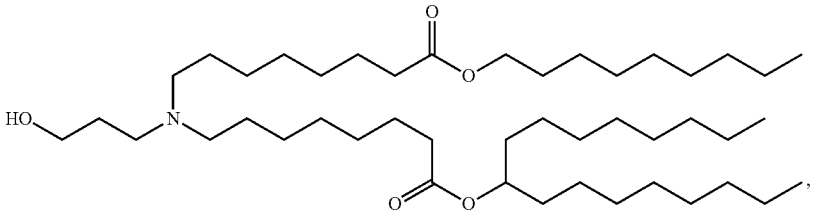

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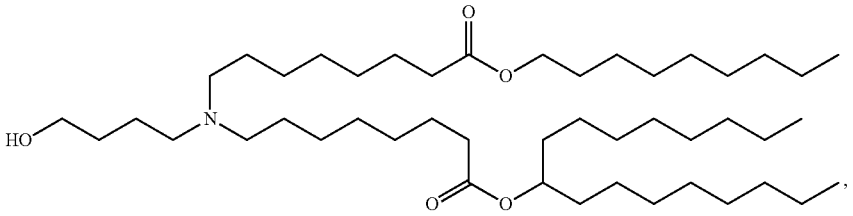

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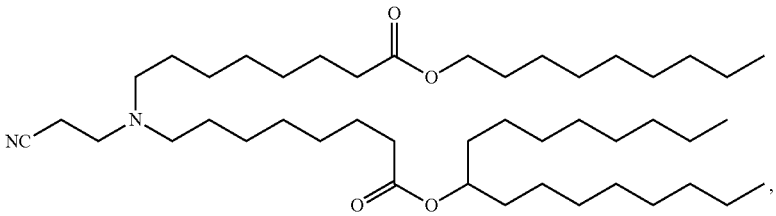

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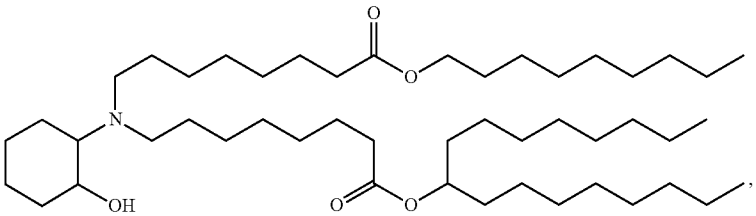

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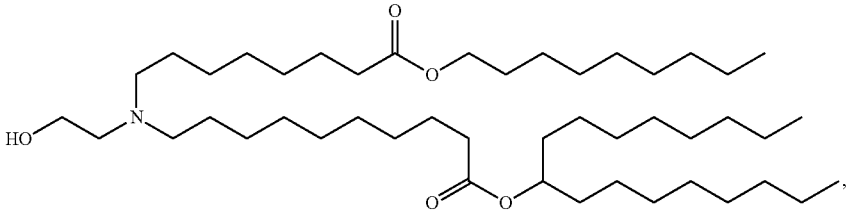

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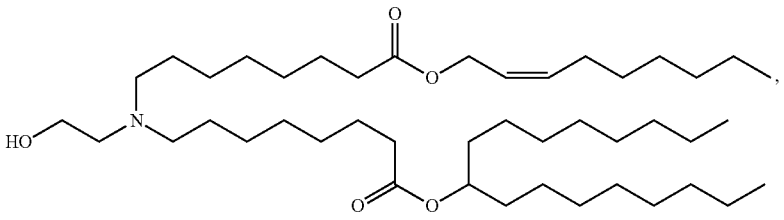

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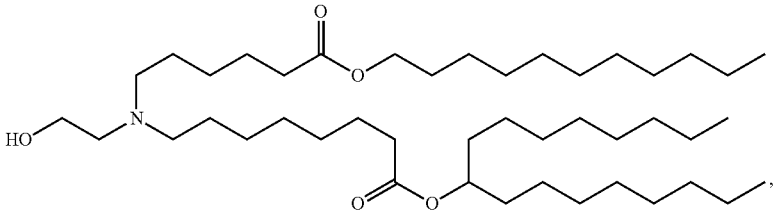

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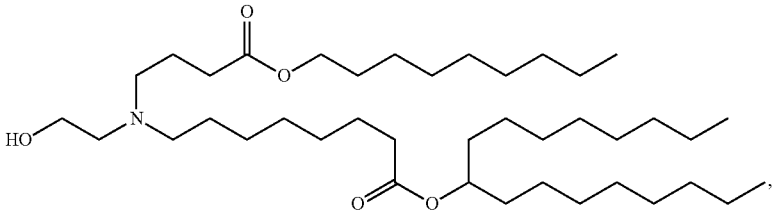

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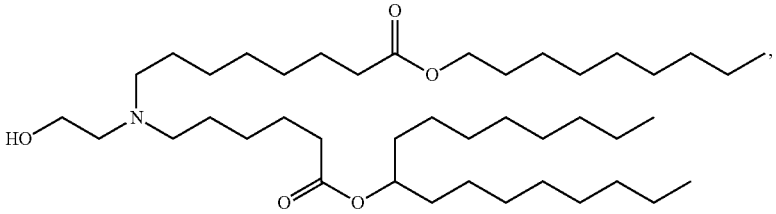

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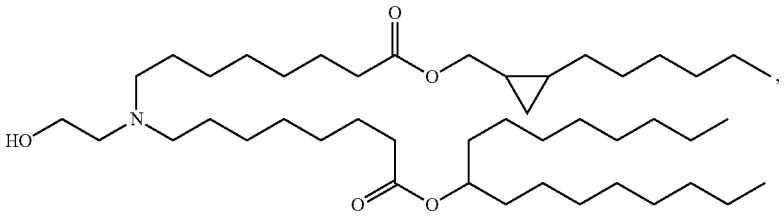

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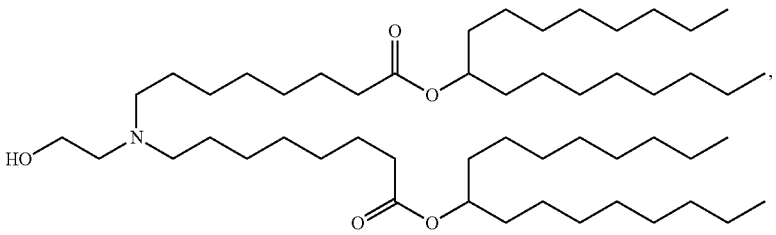

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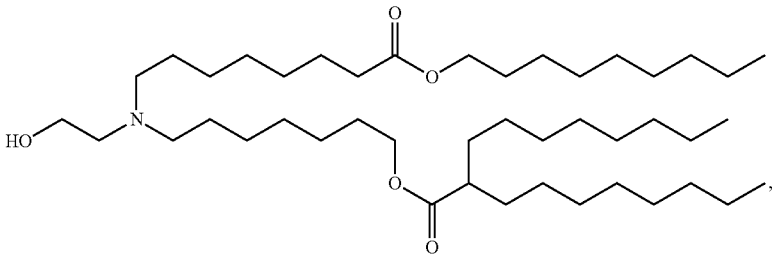

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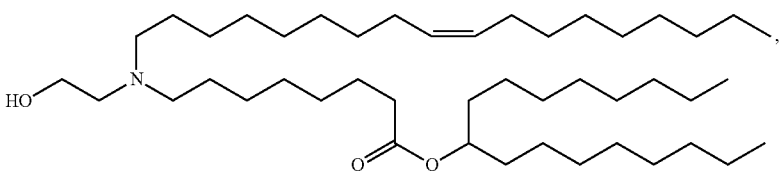

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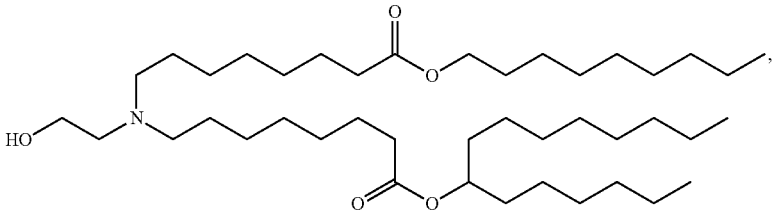

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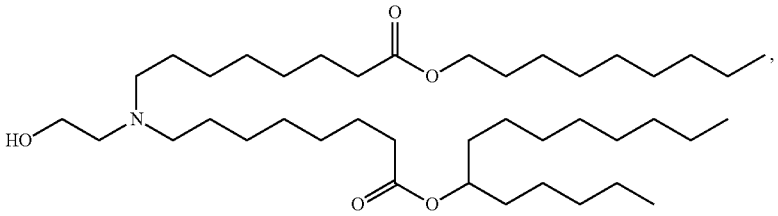

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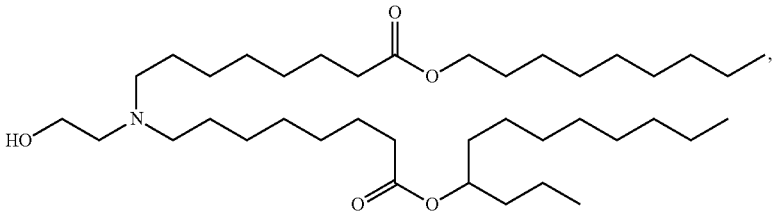

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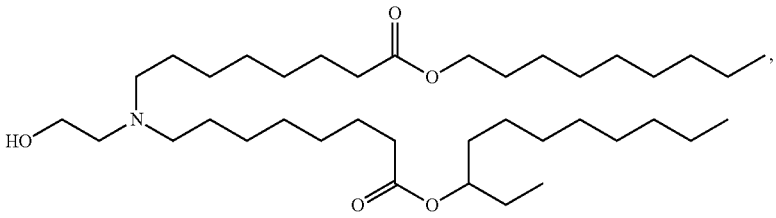

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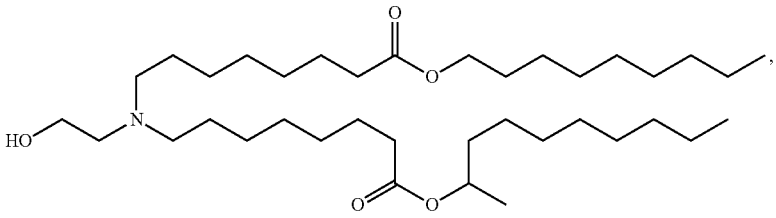

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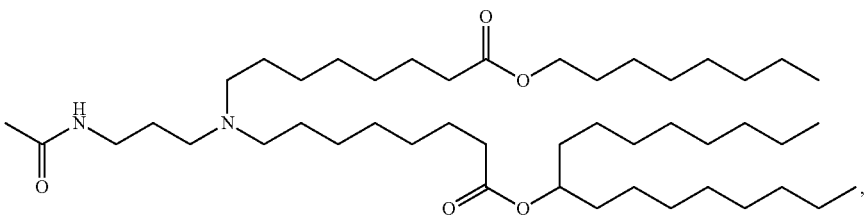

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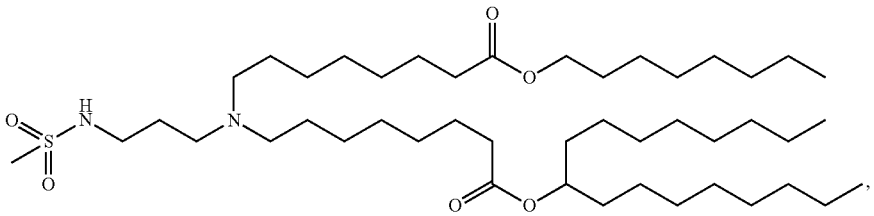

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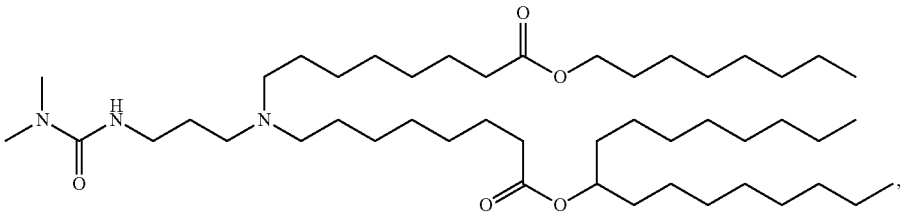

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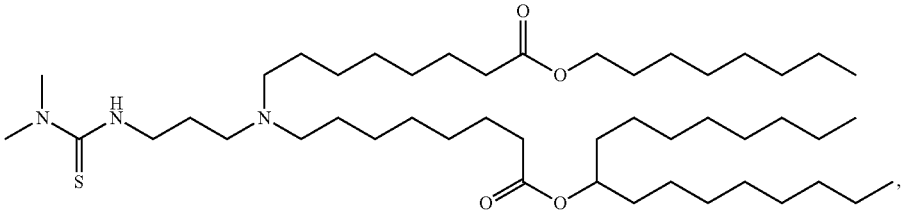

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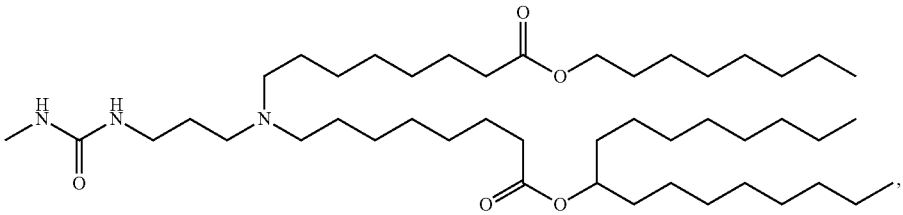

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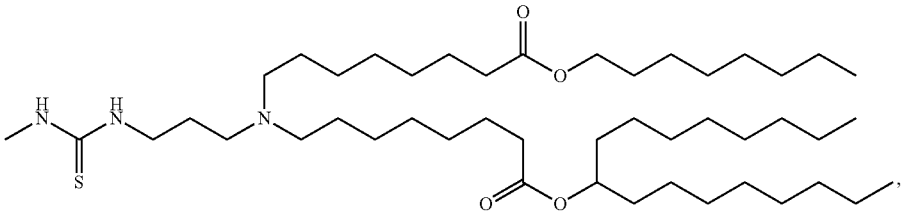

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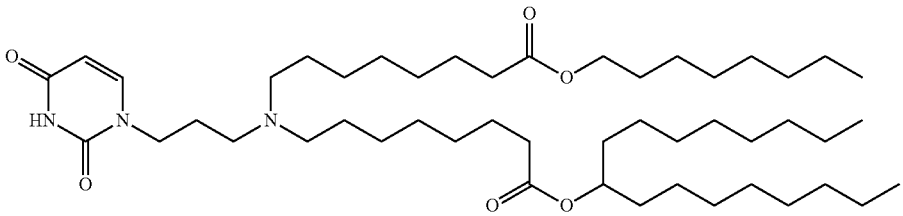

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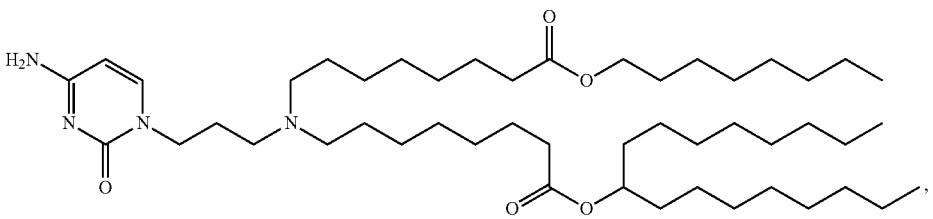

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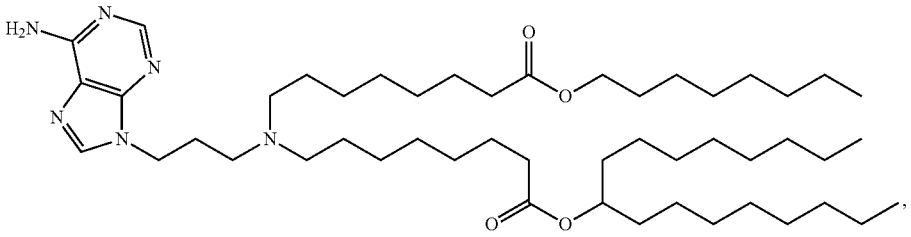

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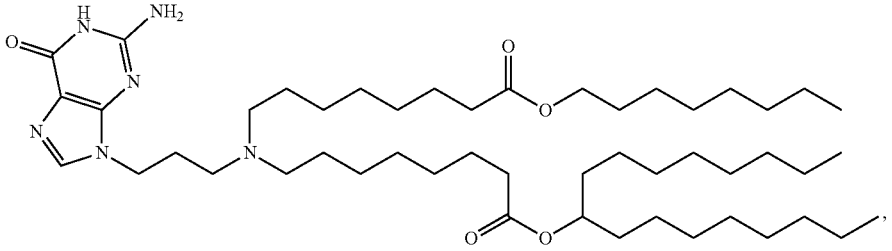

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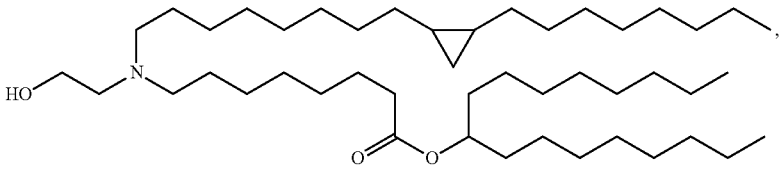

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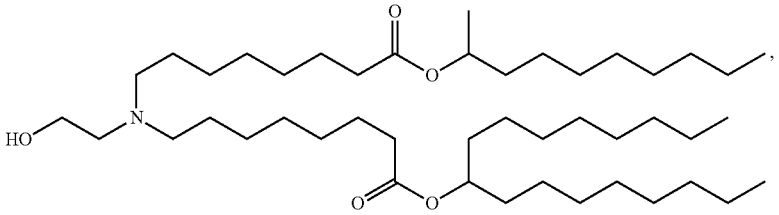

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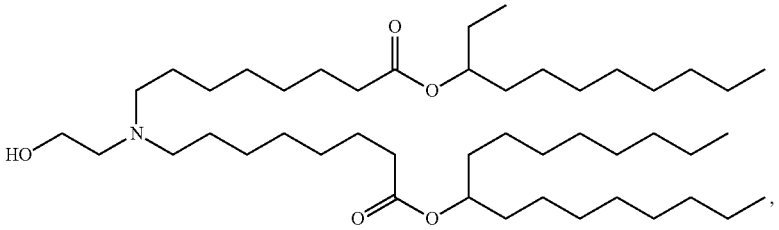

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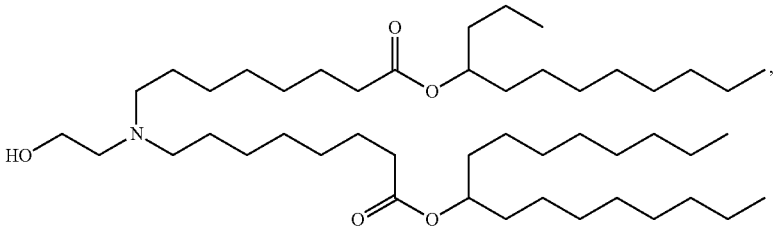

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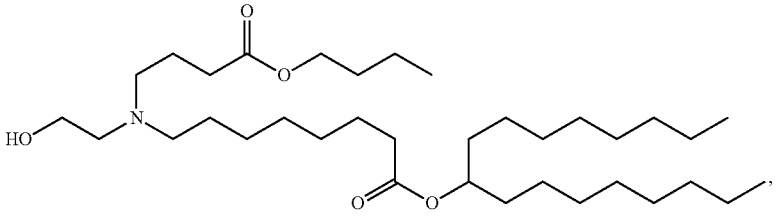

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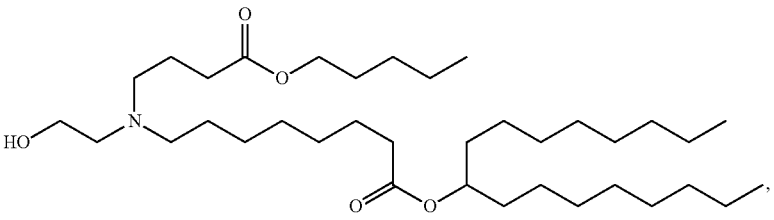

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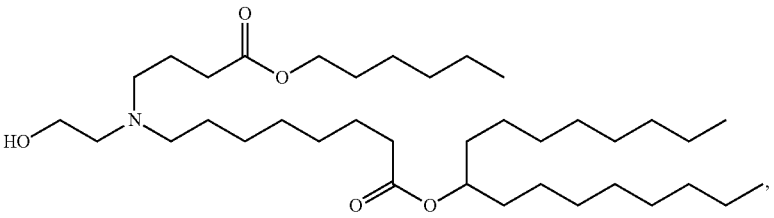

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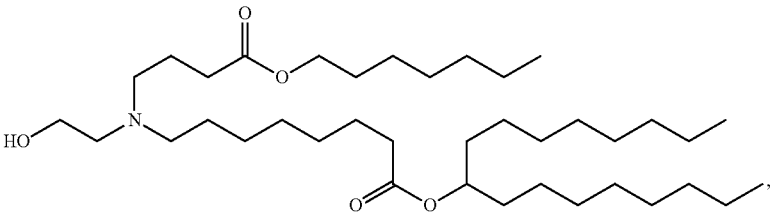

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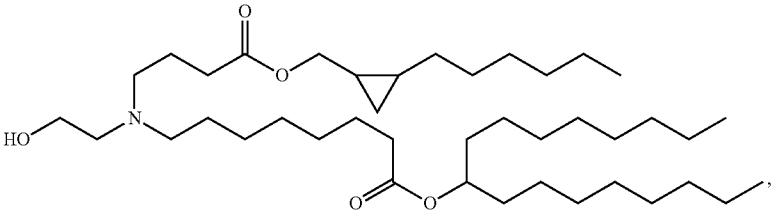
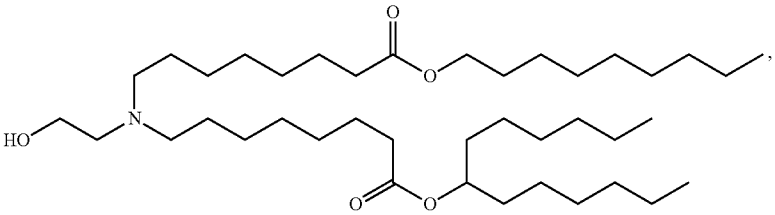
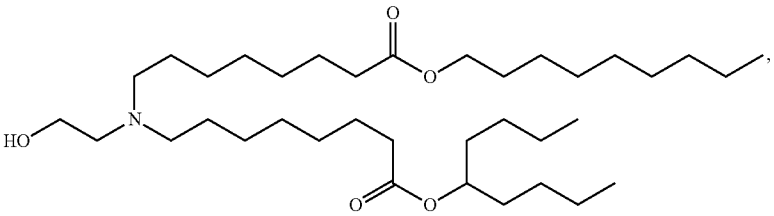


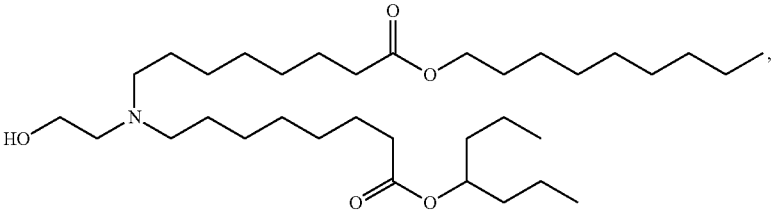
(Compound 56)



(Compound 57)



(Compound 58)



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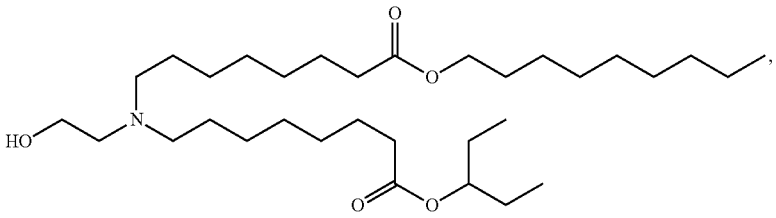
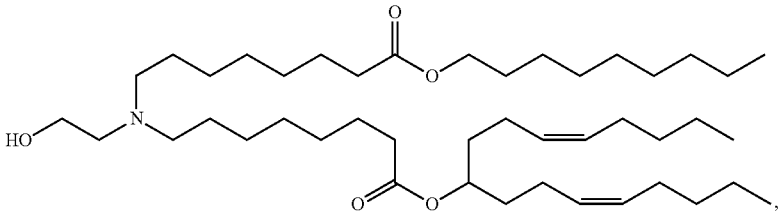
(Compound 59)

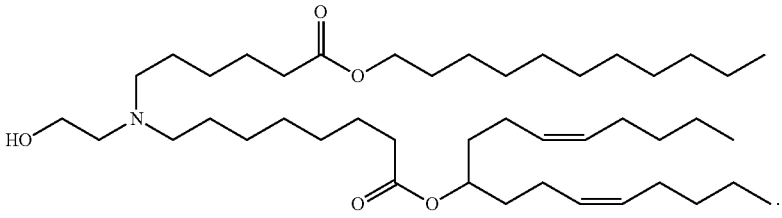


(Compound 60)



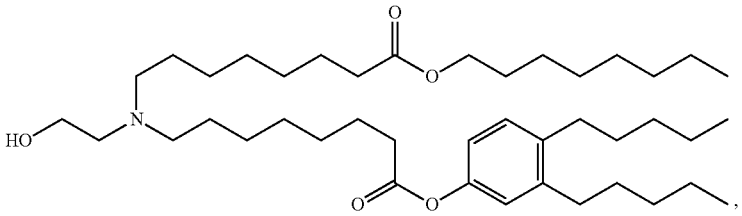
and

(Compound 61)

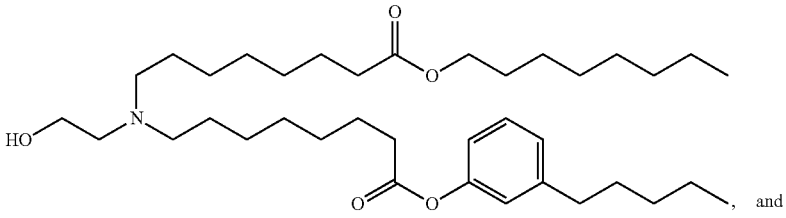


In further embodiments, the compound of Formula (I) is selected from the group consisting of:

(Compound 62)

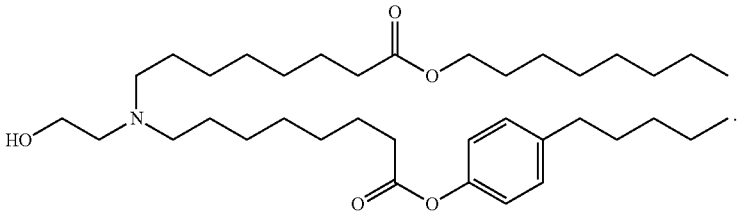


(Compound 63)

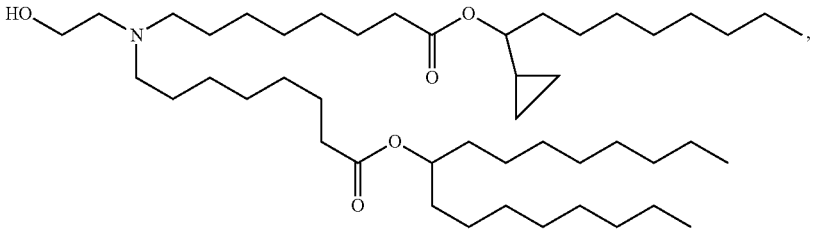


and

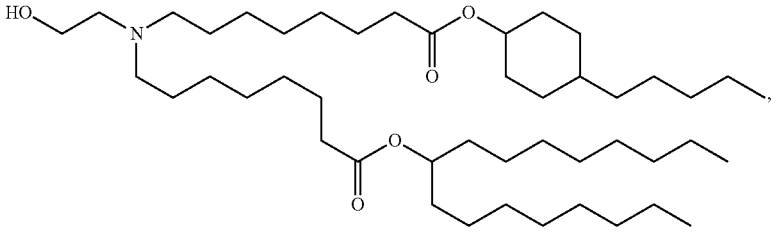
(Compound 64)



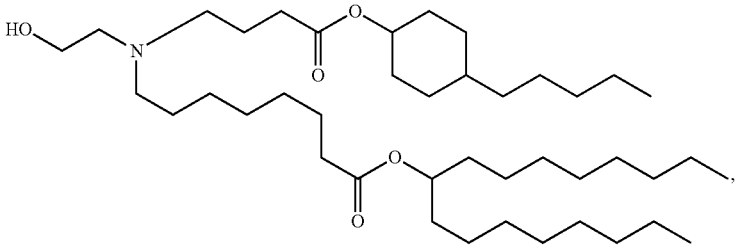
In some embodiments, the compound of Formula (I) is selected from the group consisting of:



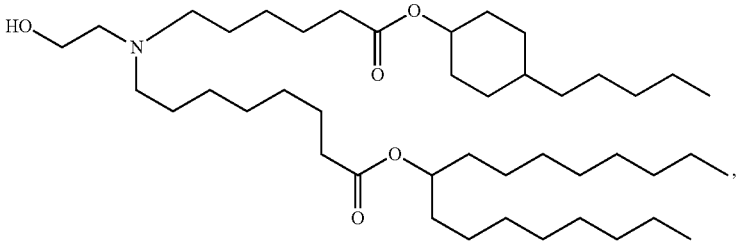
(Compound 65)



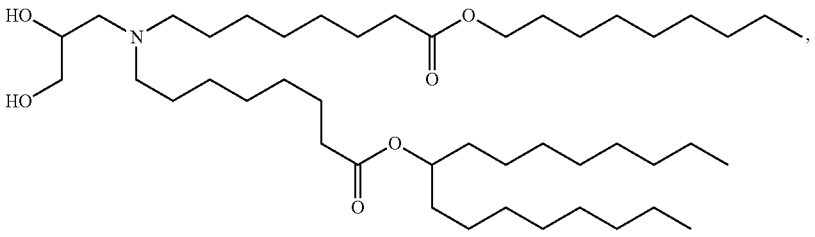
(Compound 66)



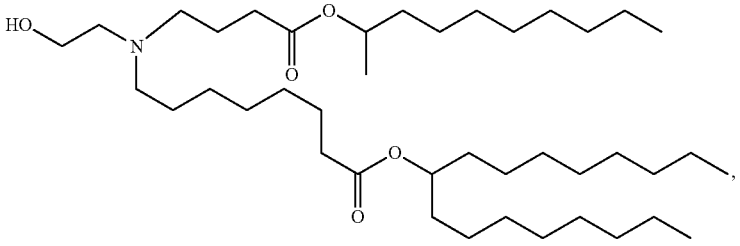
(Compound 67)



(Compound 68)



(Compound 69)



(Compound 70)

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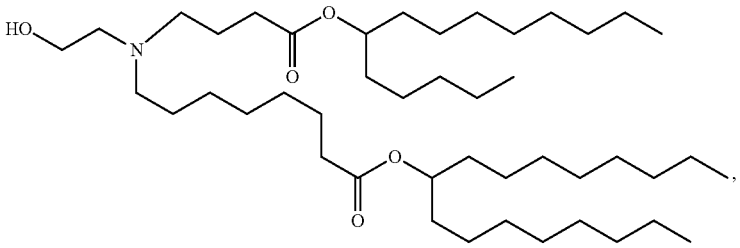
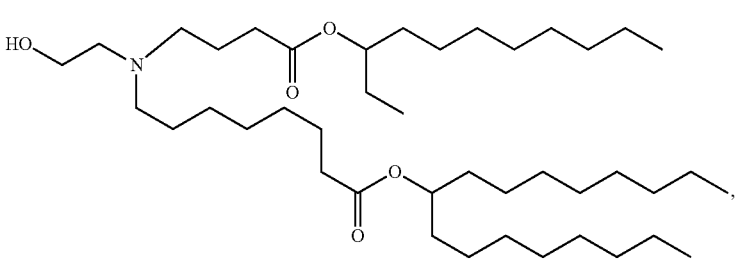
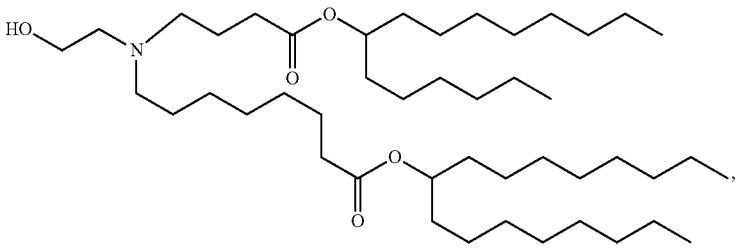
(Compound 71)



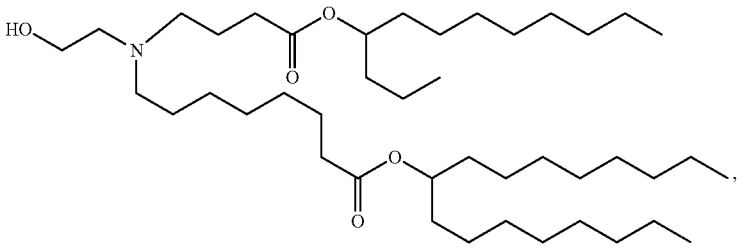
(Compound 72)



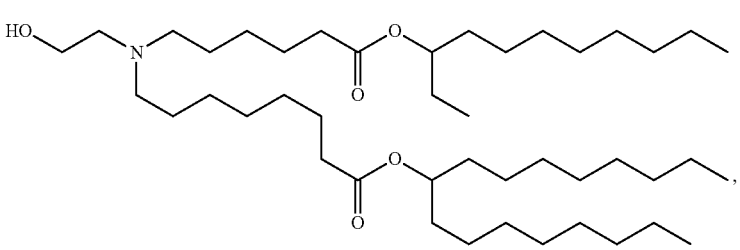
(Compound 73)



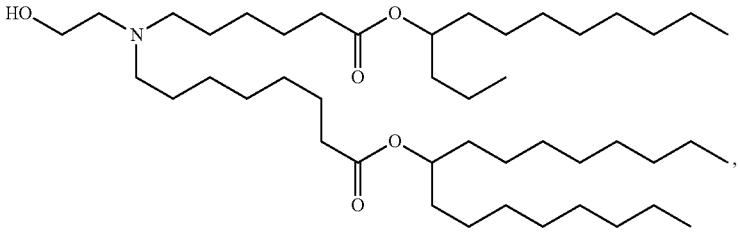
(Compound 74)



(Compound 75)



(Compound 76)



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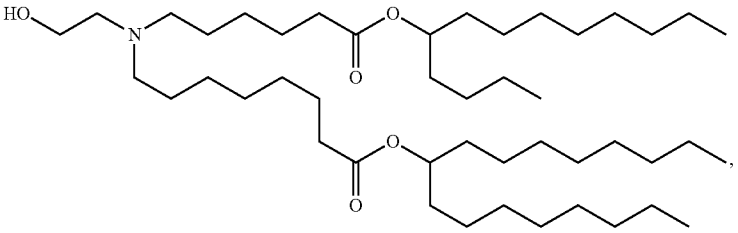
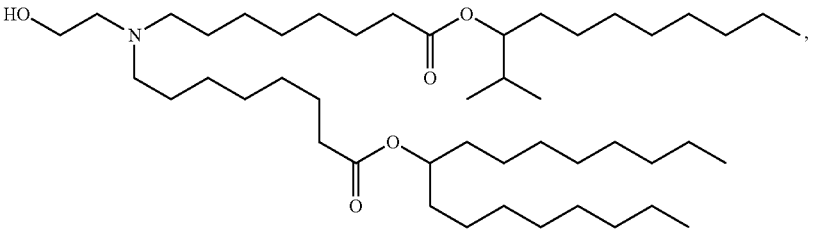
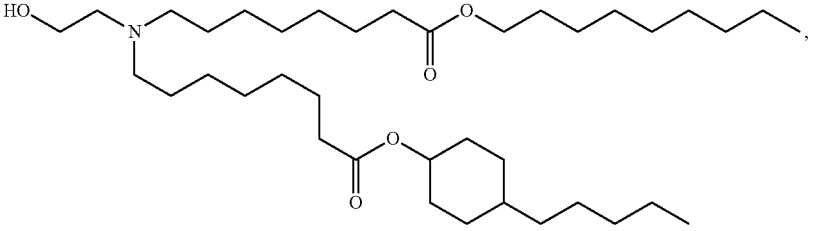
(Compound 77)



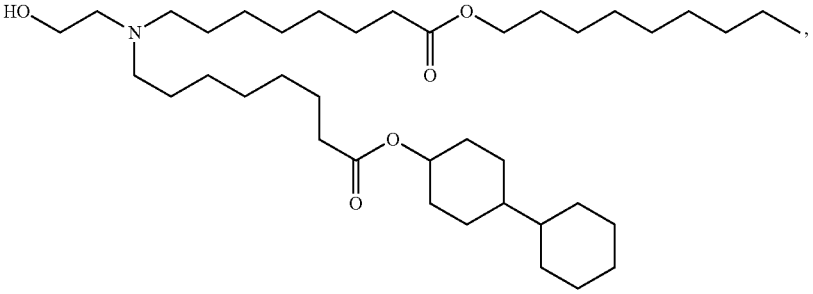
(Compound 78)



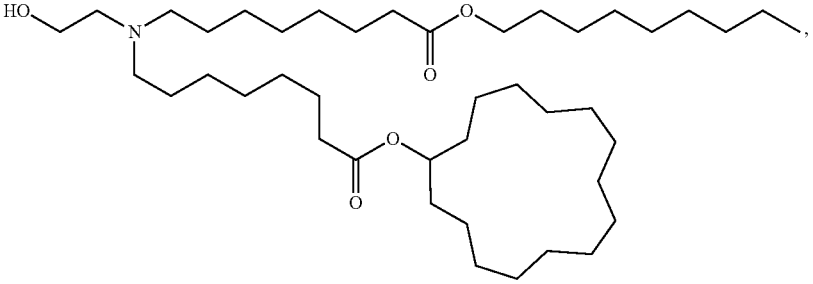
(Compound 79)



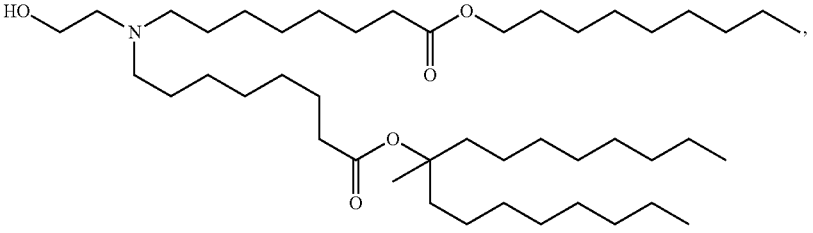
(Compound 80)



(Compound 81)



(Compound 82)



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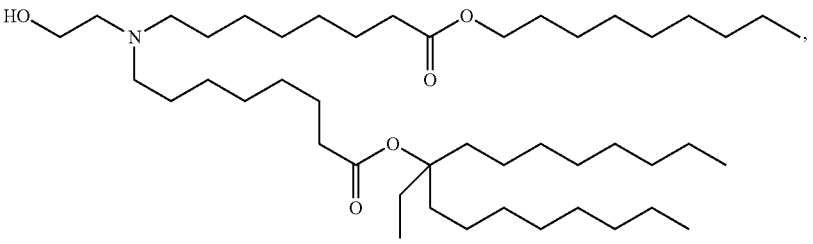
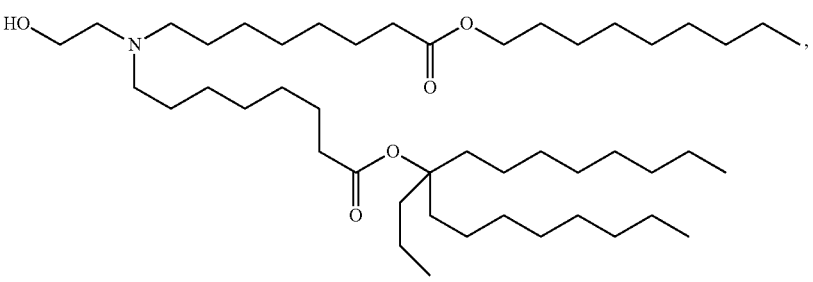
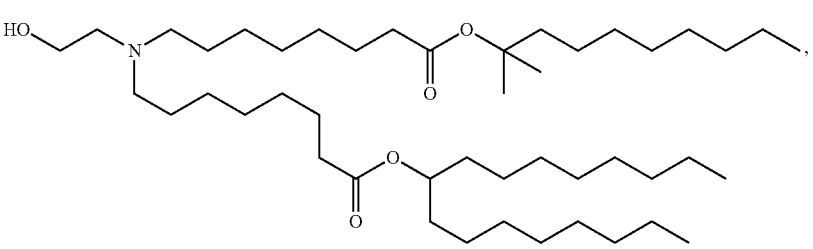
(Compound 83)



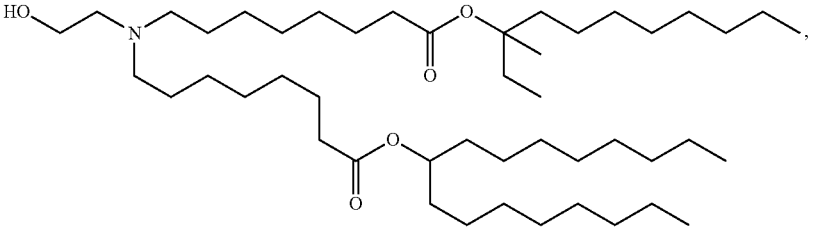
(Compound 84)



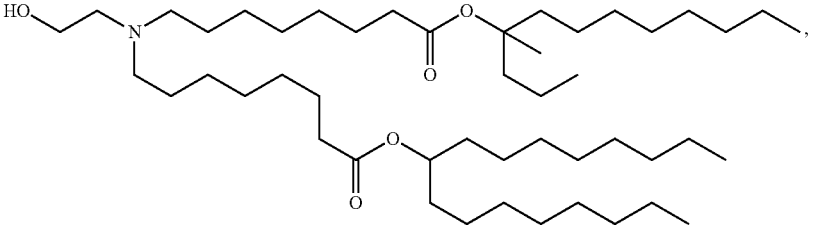
(Compound 85)



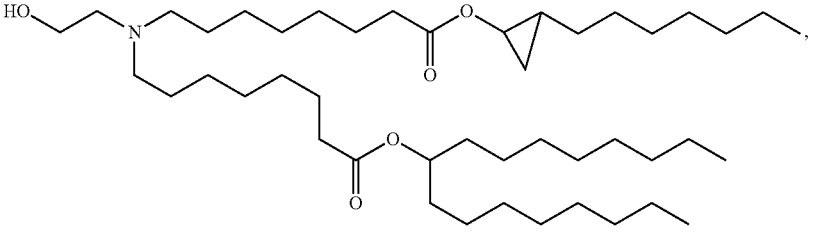
(Compound 86)



(Compound 87)



(Compound 88)



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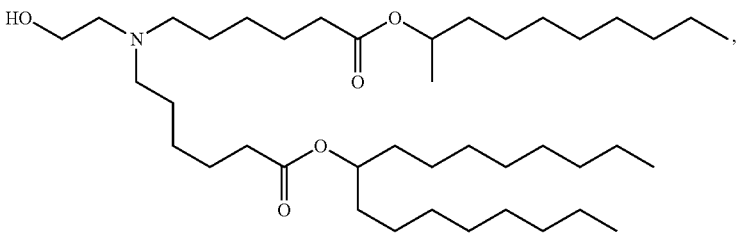
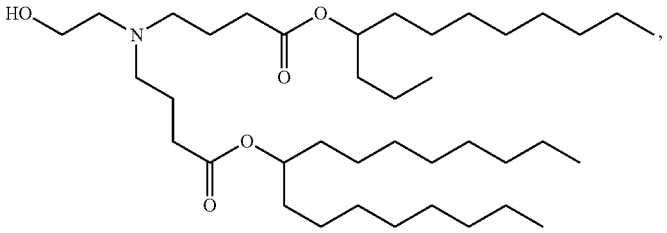
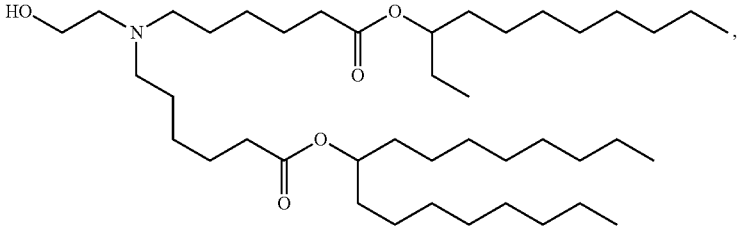
(Compound 89)



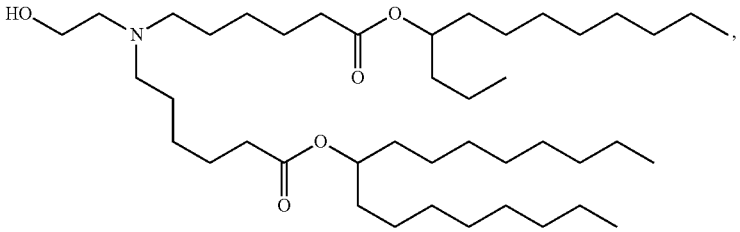
(Compound 90)



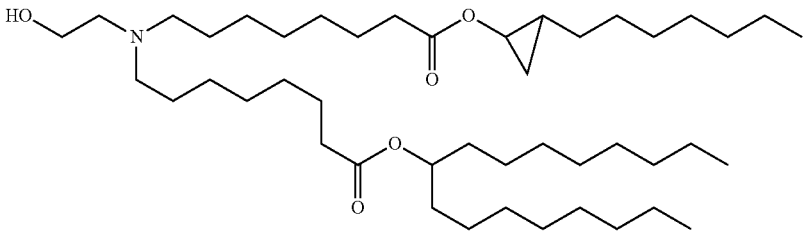
(Compound 91)



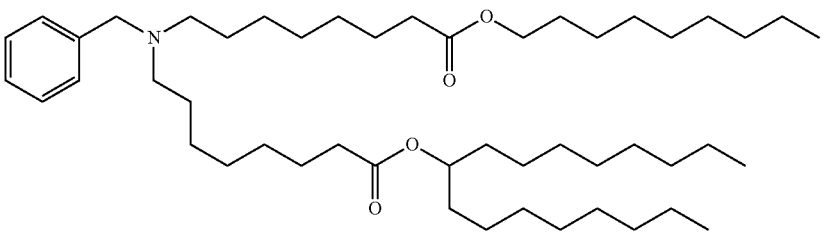
(Compound 92)



(Compound 93)



(Compound 94)



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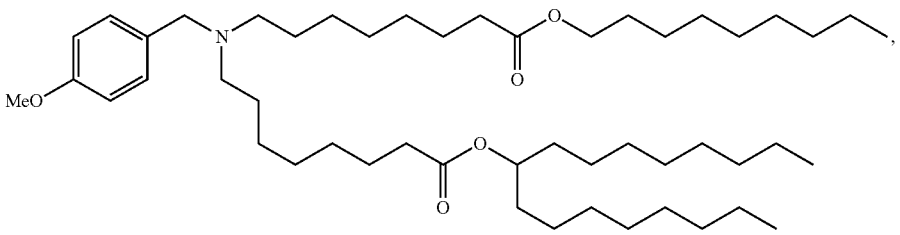
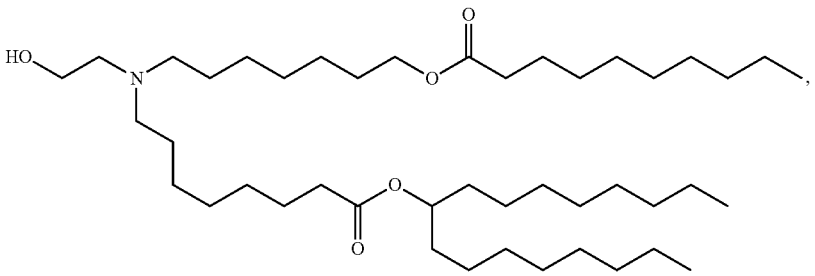
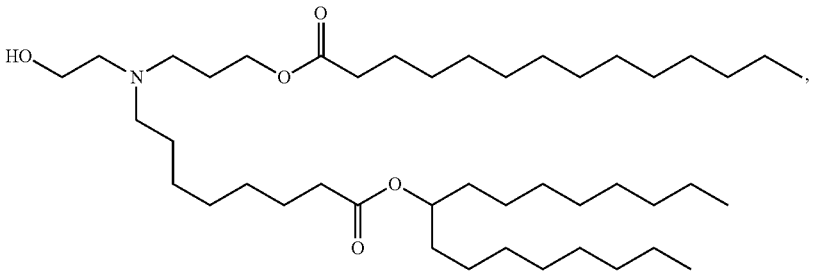
(Compound 95)



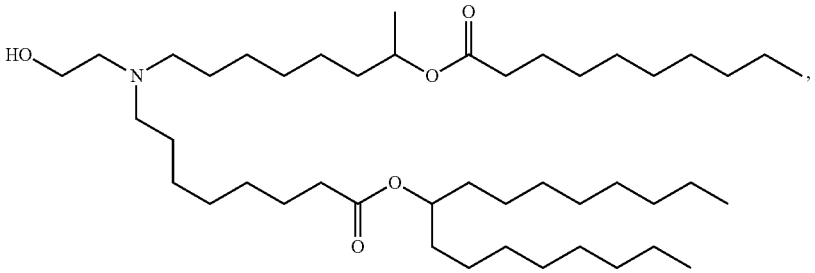
(Compound 96)



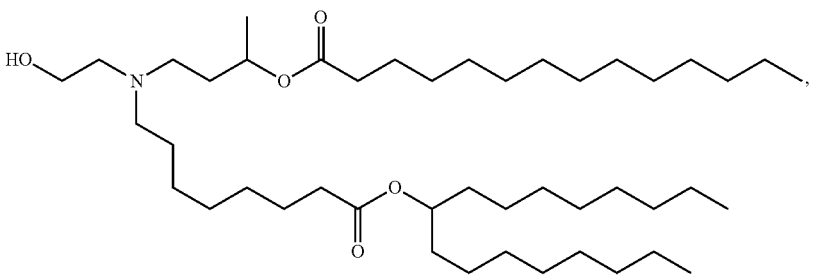
(Compound 97)



(Compound 98)



(Compound 99)



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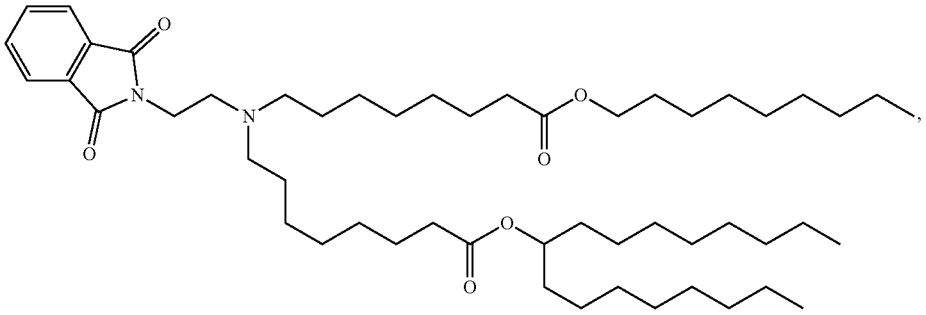
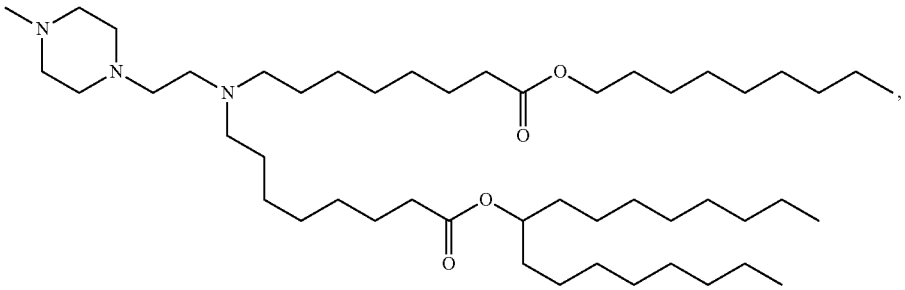
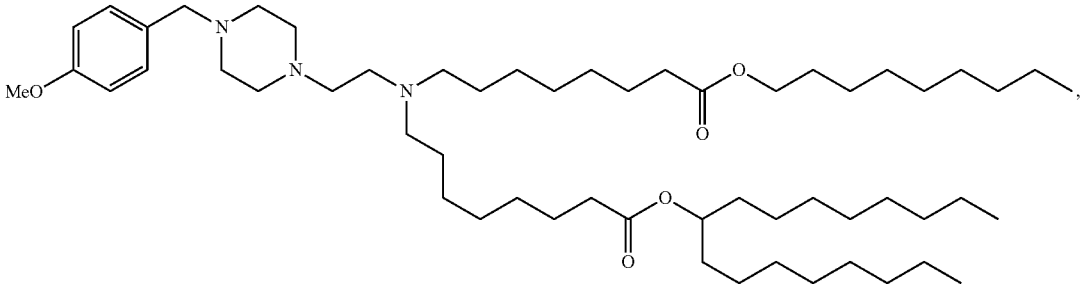
(Compound 100)



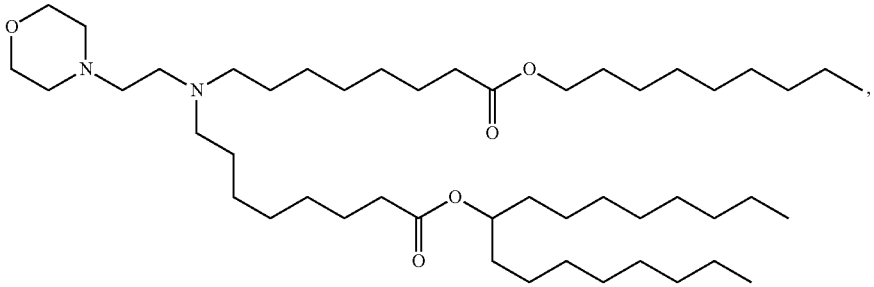
(Compound 101)



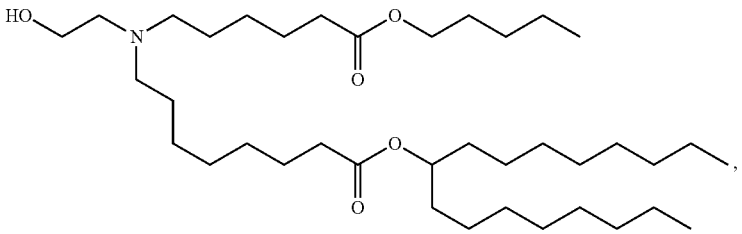
(Compound 102)



(Compound 103)



(Compound 104)



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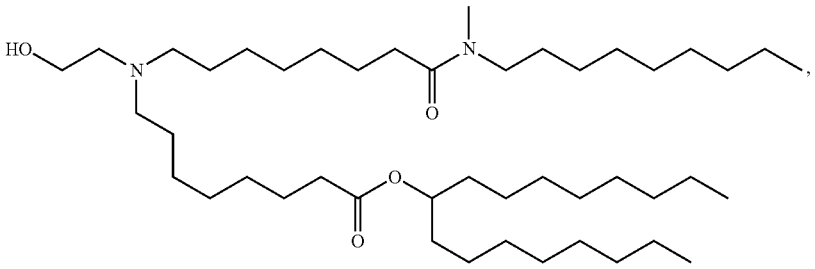

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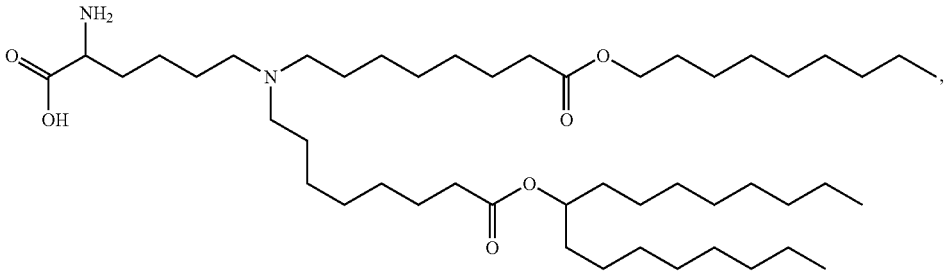

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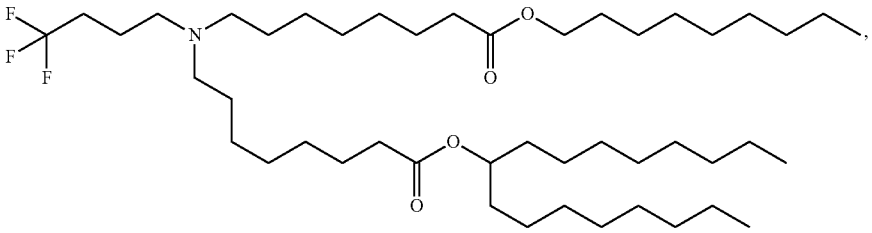

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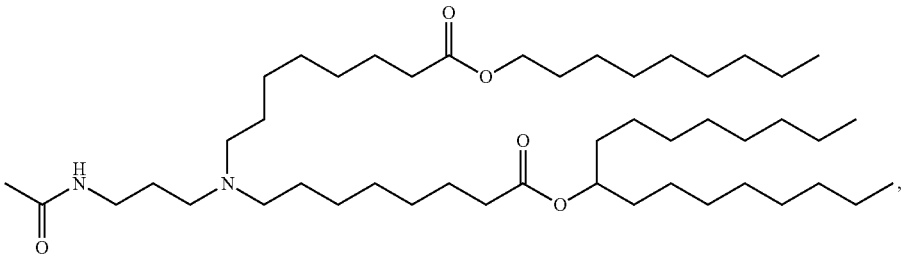

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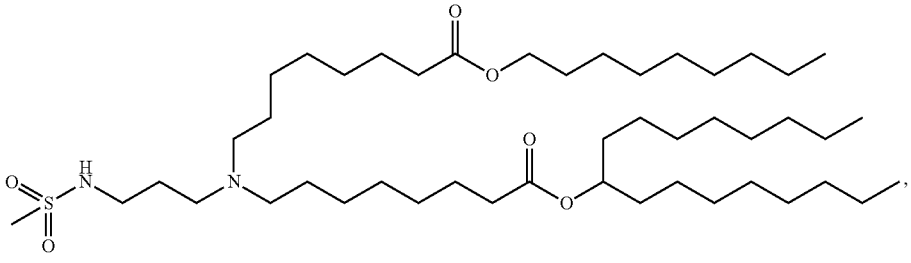

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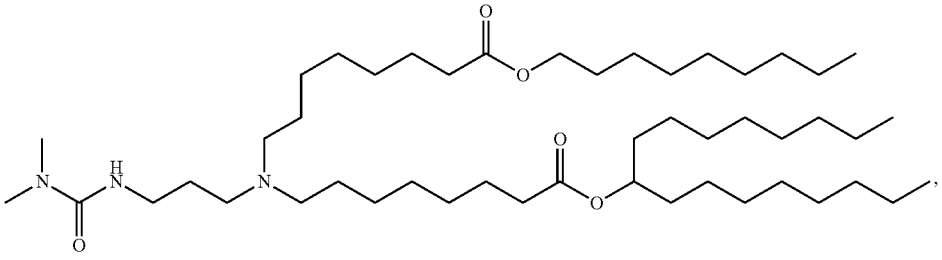

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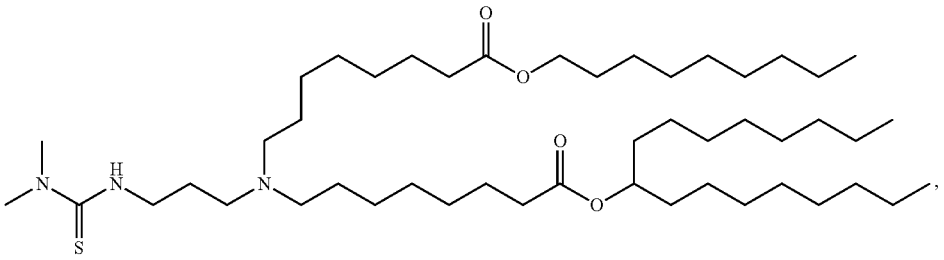

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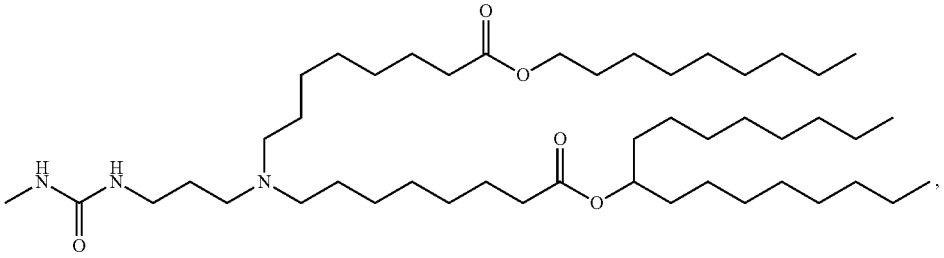

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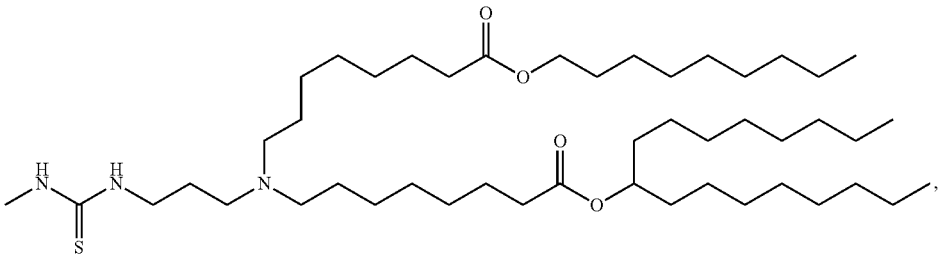

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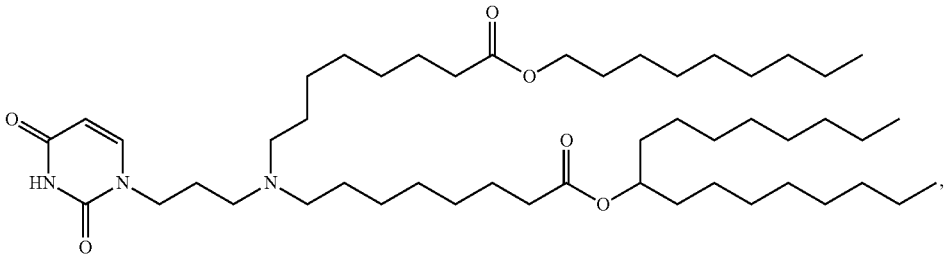

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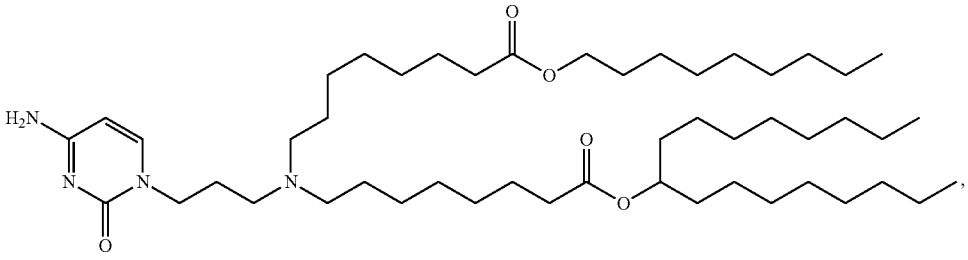

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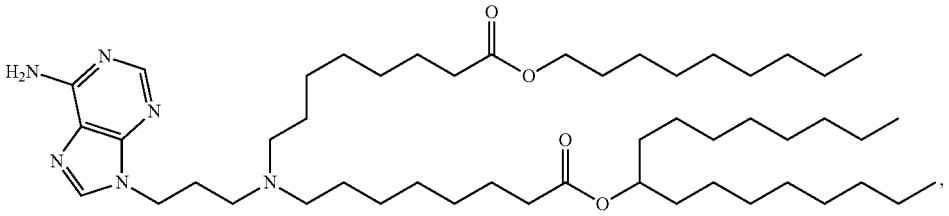

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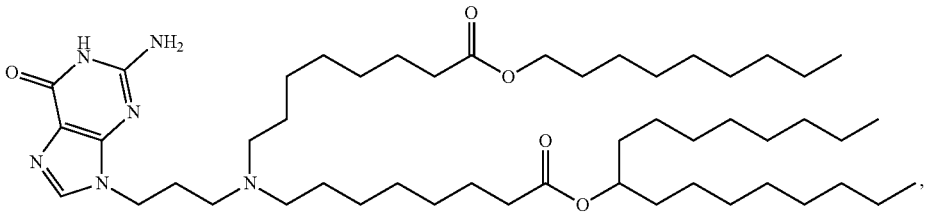

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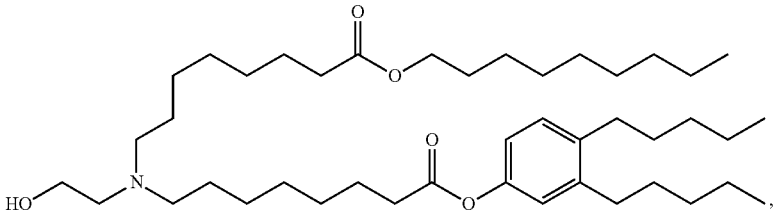

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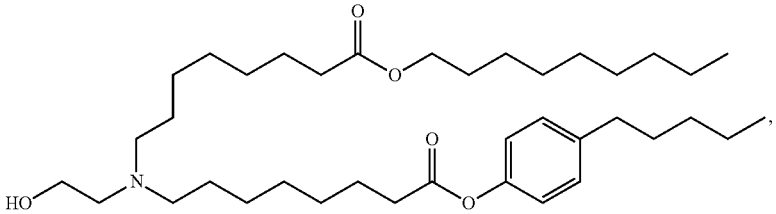

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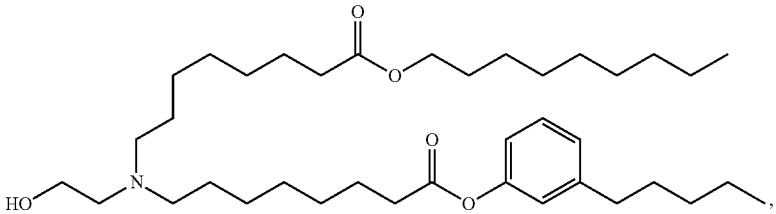

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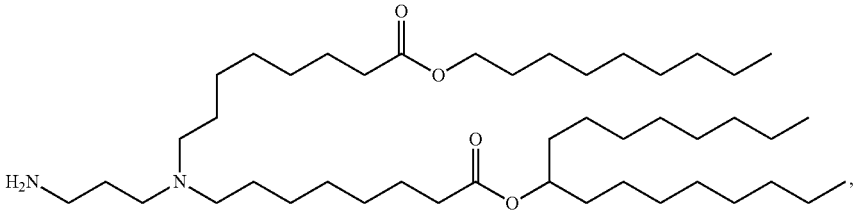

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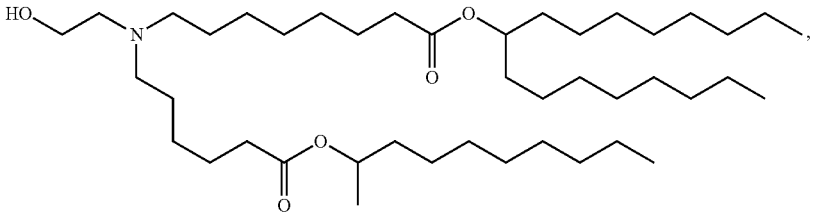

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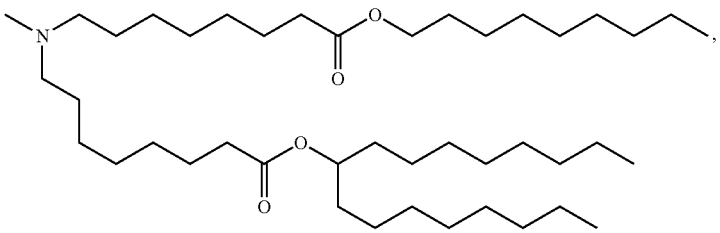

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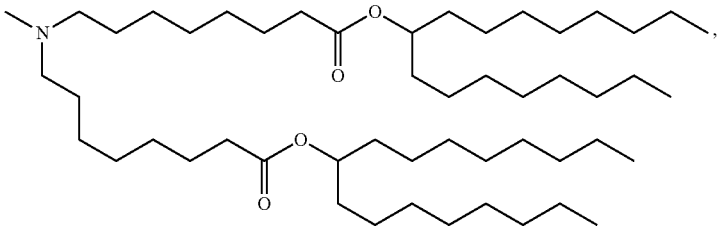

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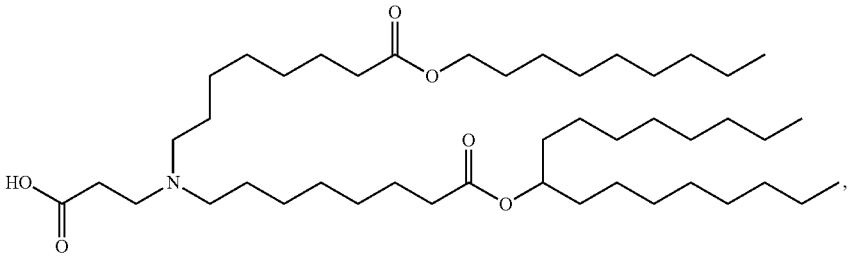

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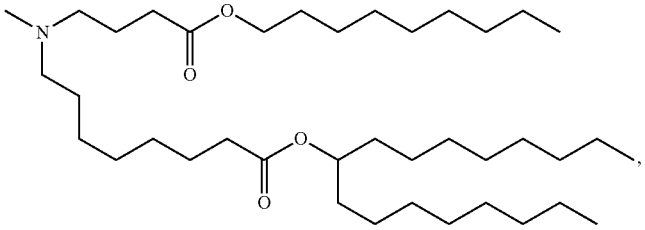

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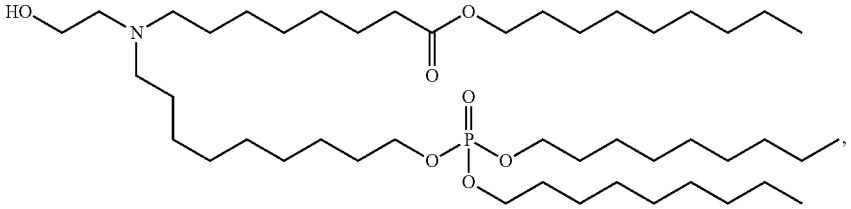

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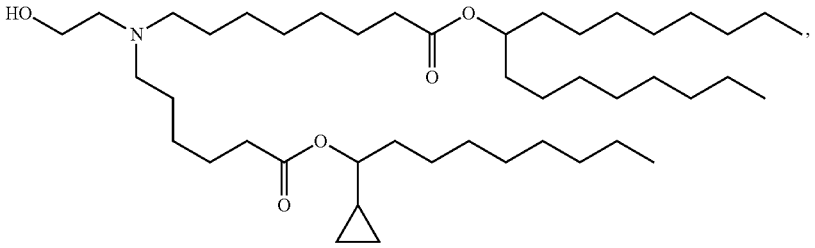

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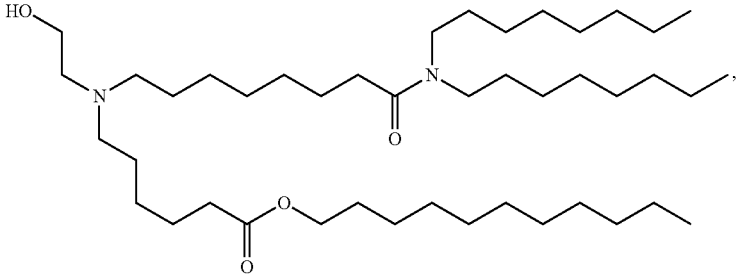

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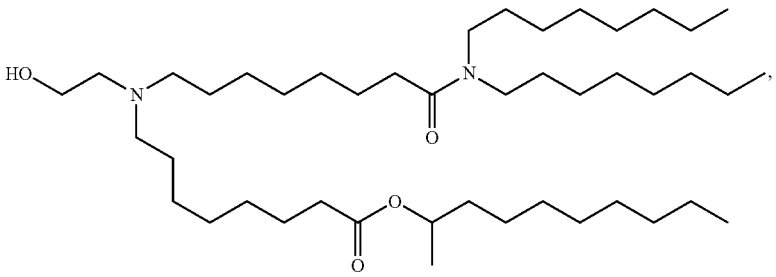

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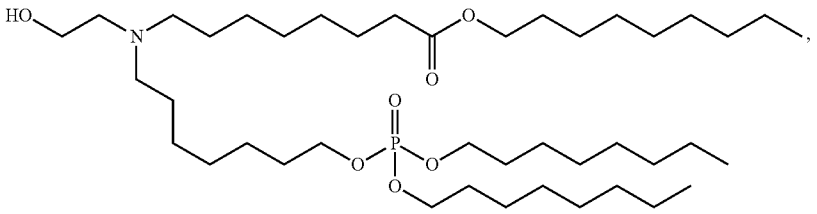

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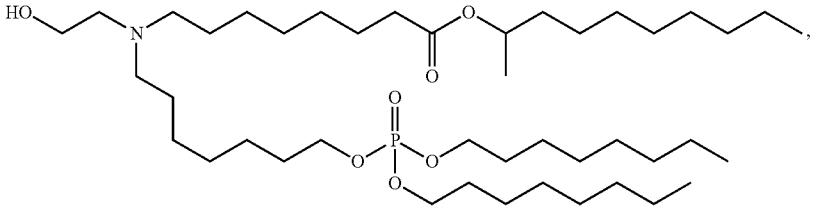

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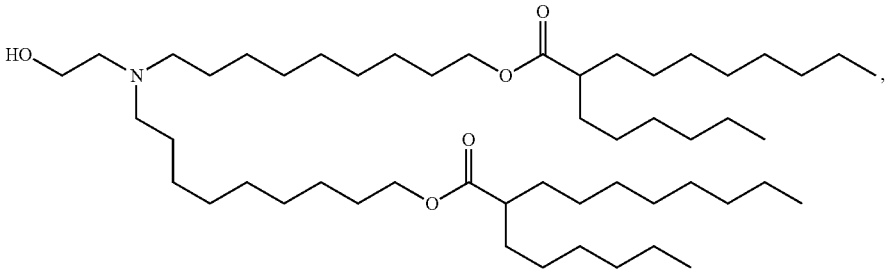

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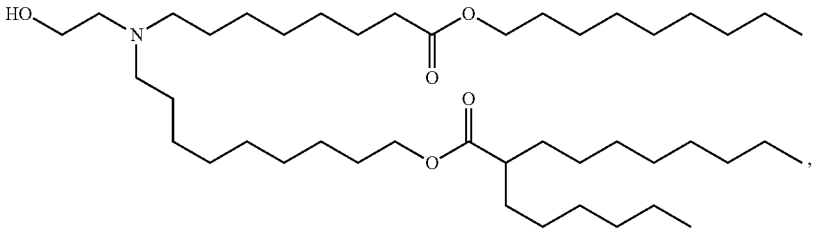

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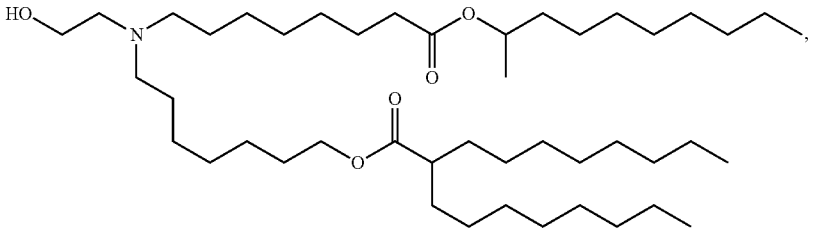

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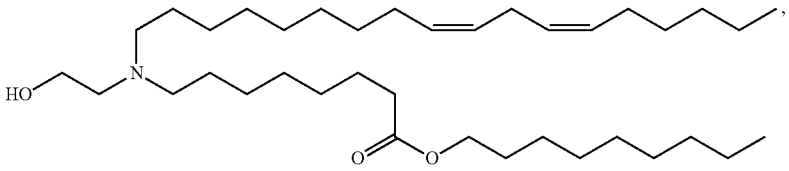

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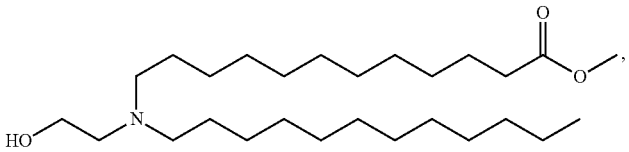

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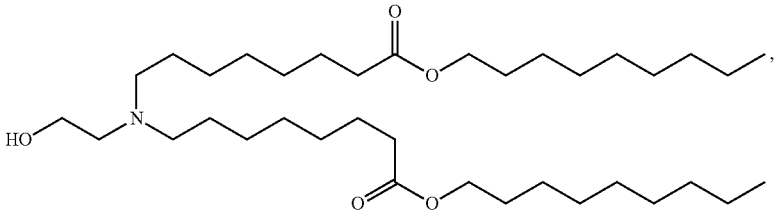

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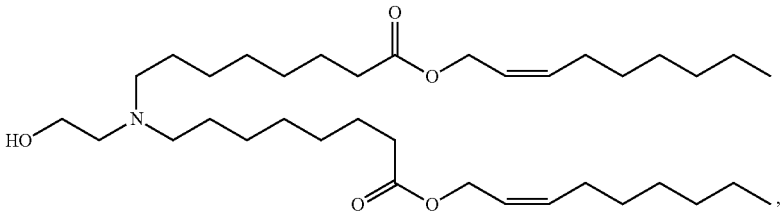

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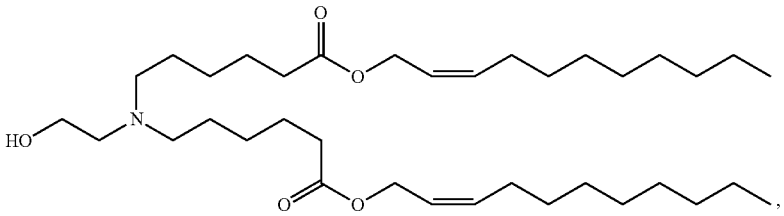

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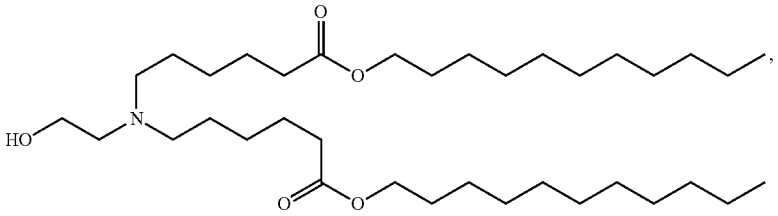

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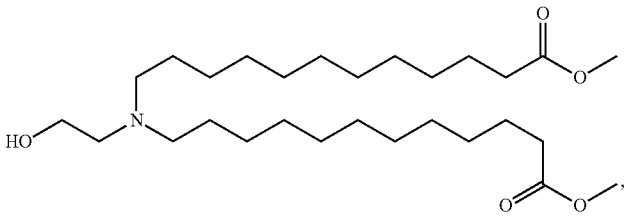

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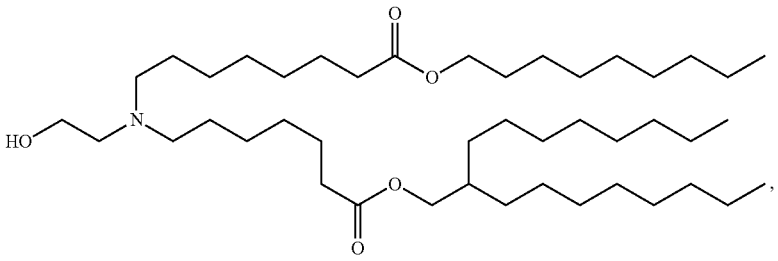

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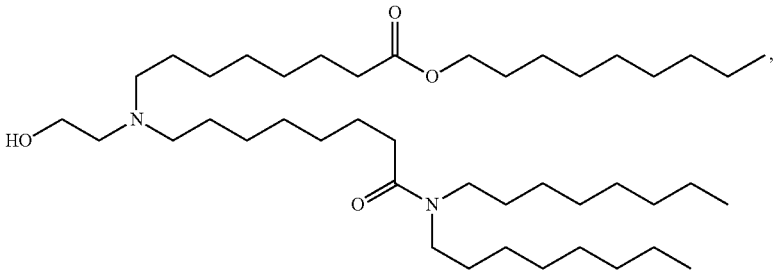

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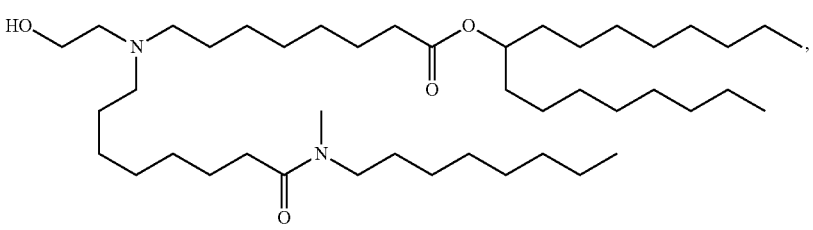

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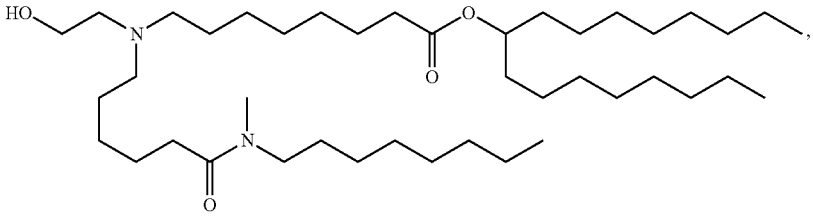

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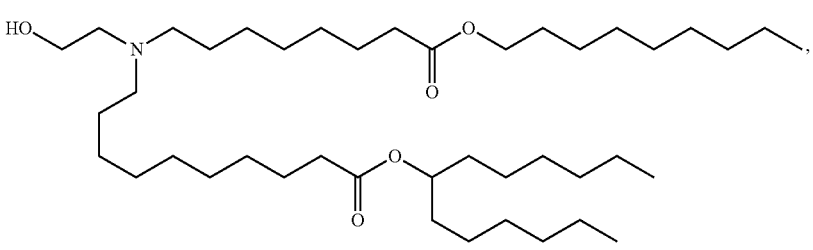

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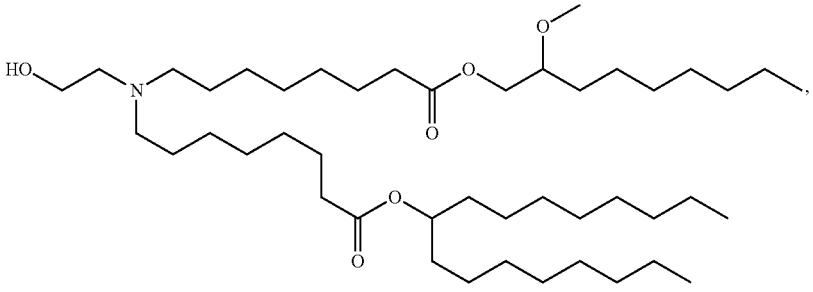

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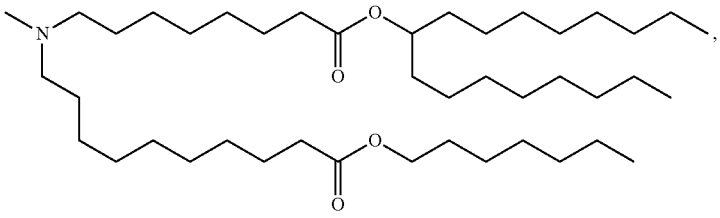

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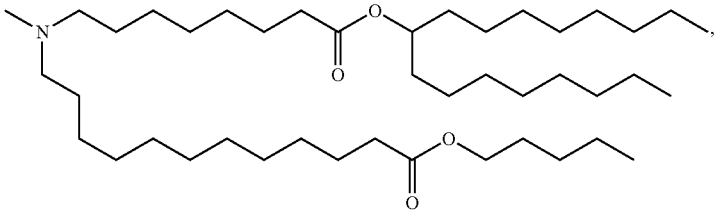

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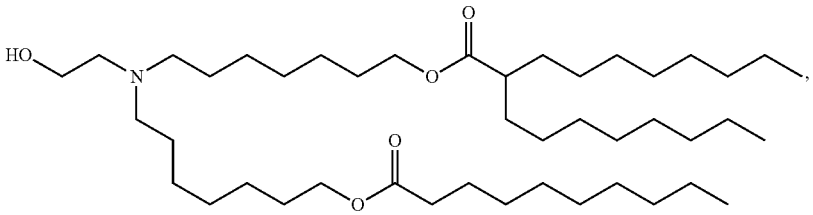

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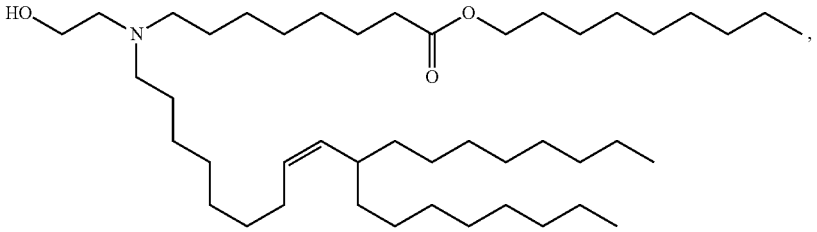

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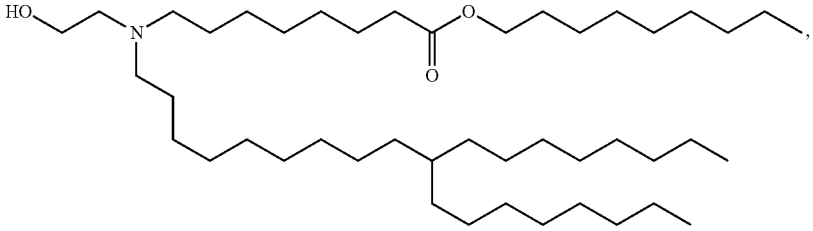

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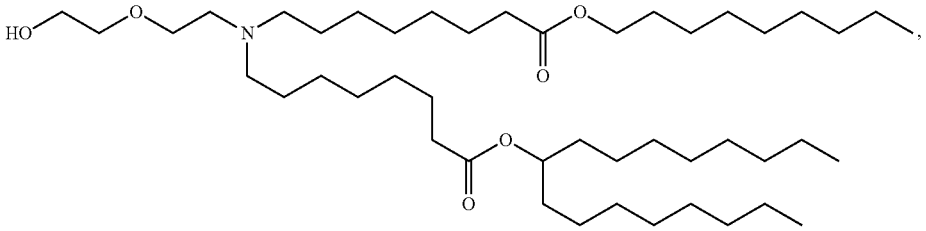

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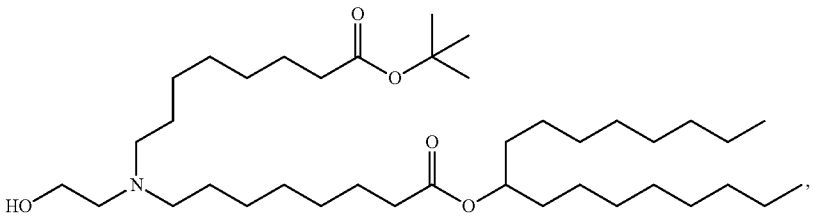

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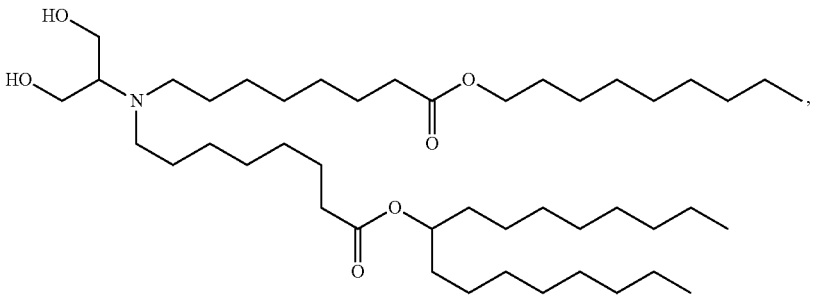

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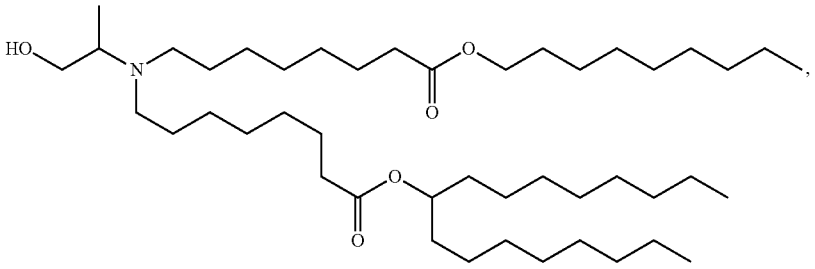

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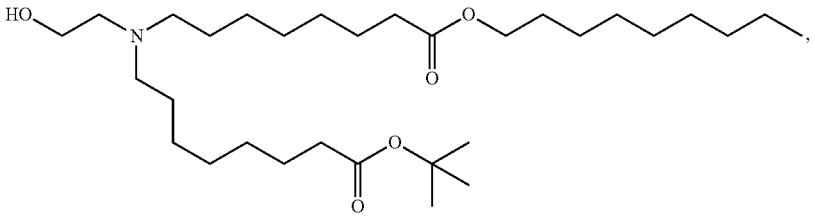

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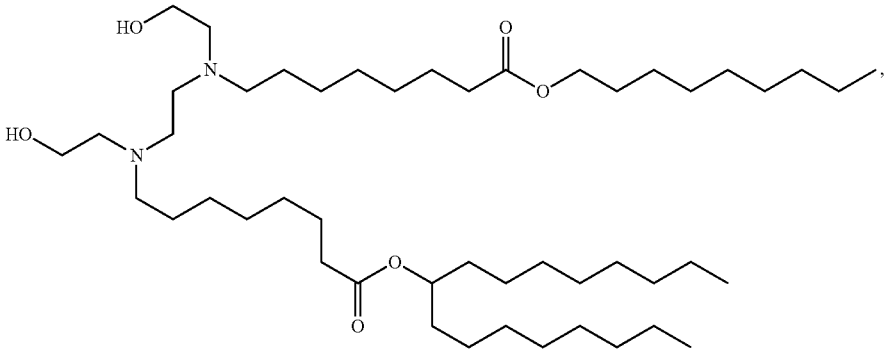

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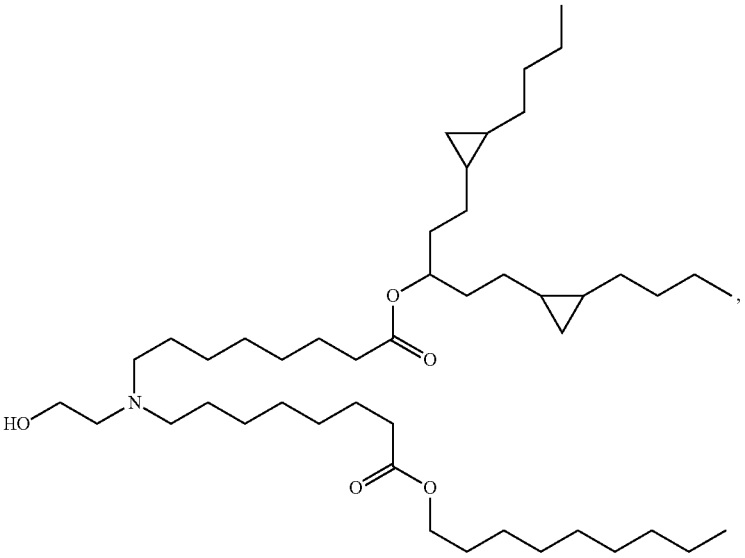

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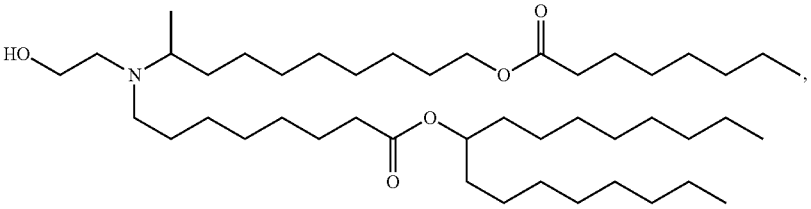

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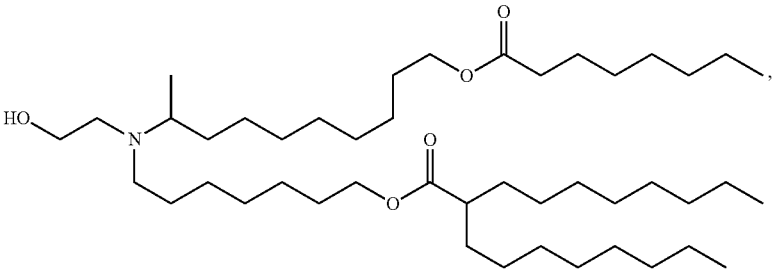

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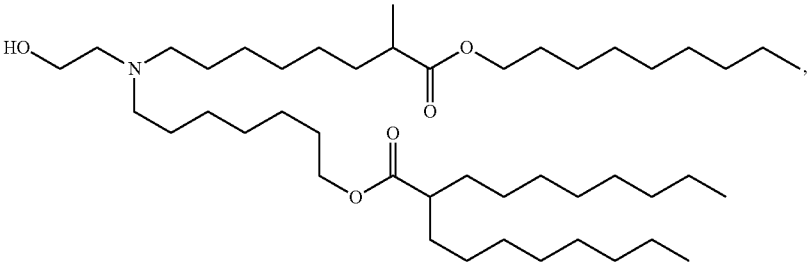

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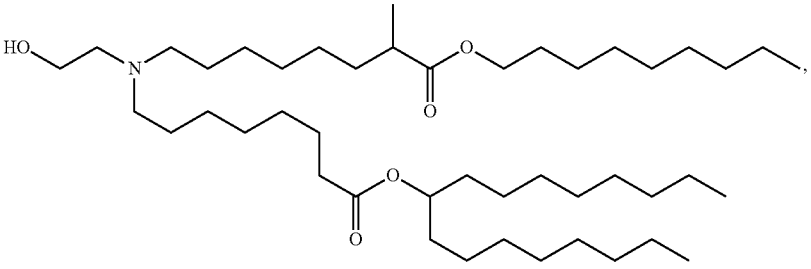

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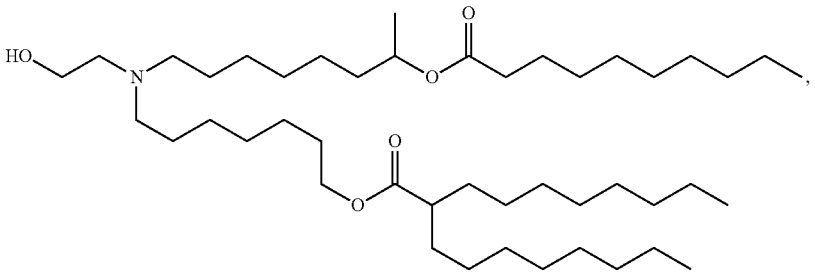

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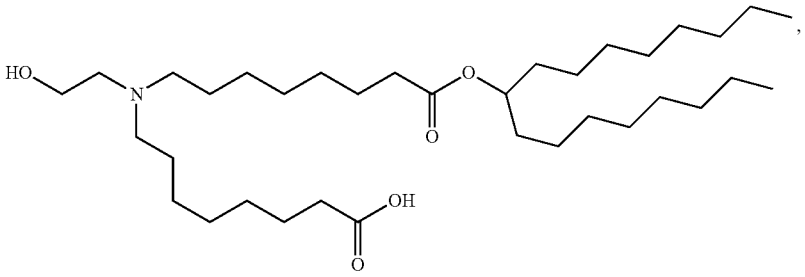

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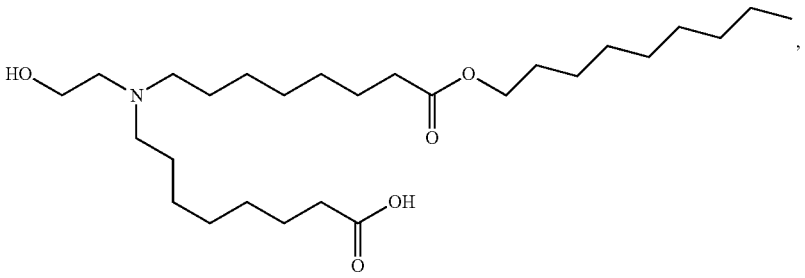

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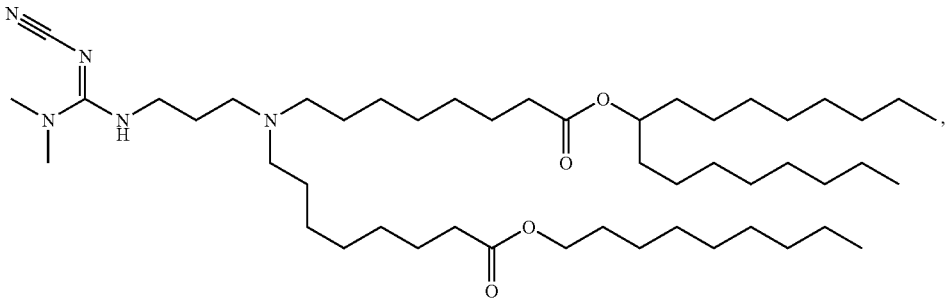

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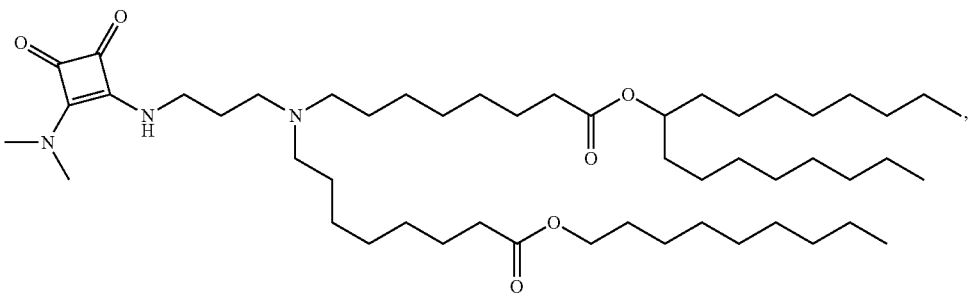

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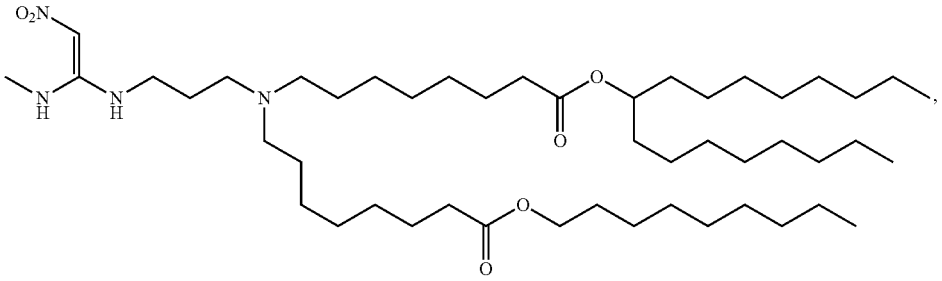

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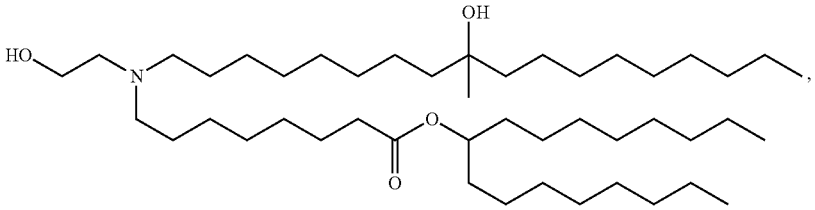

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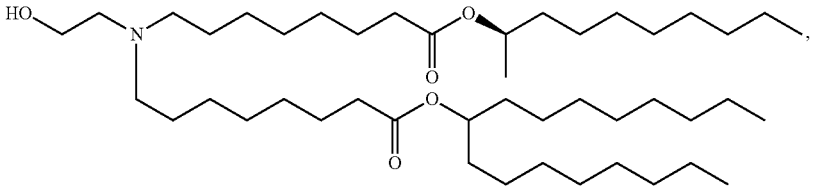

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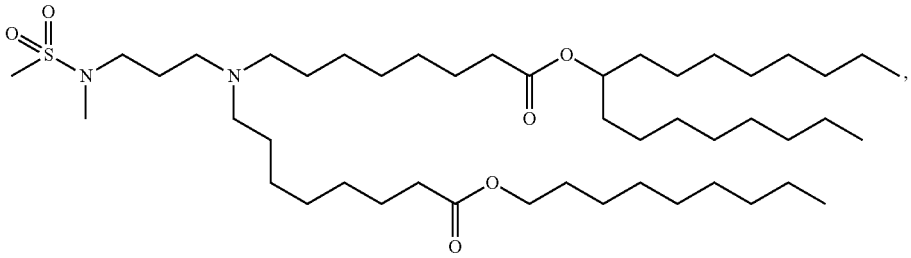

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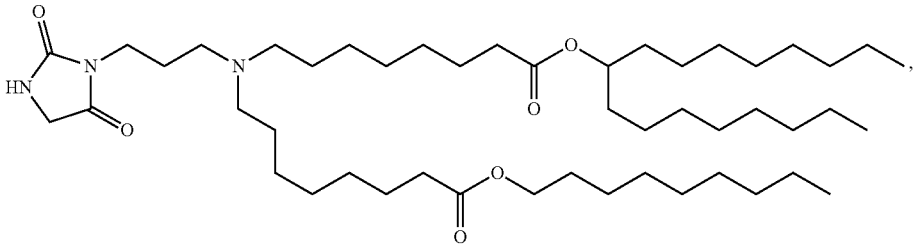

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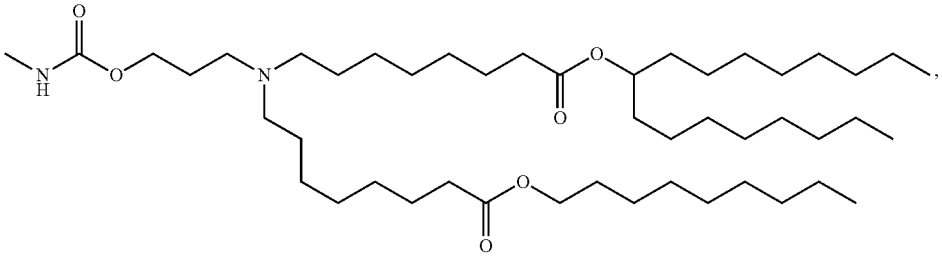

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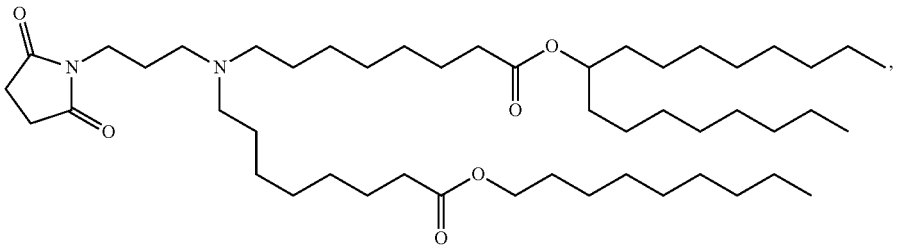

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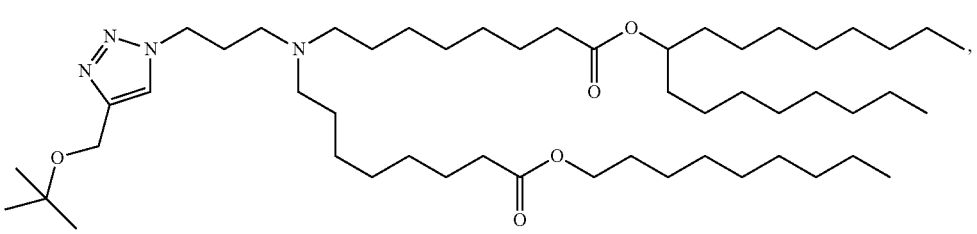

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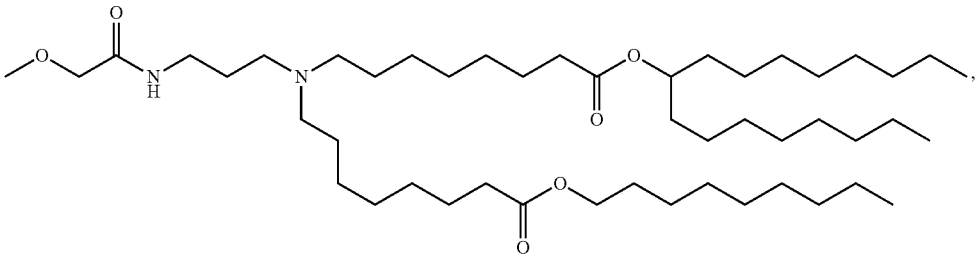

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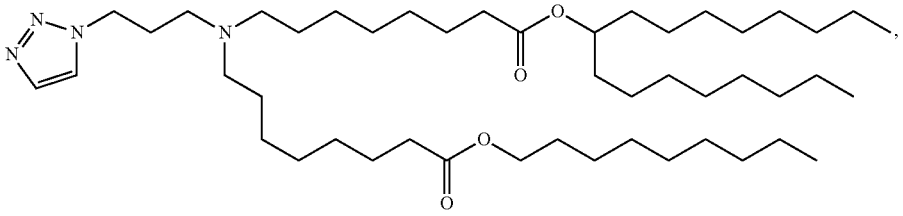

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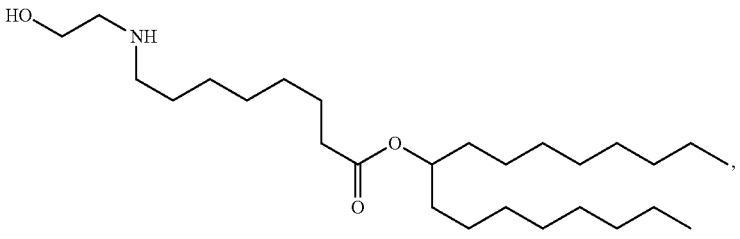

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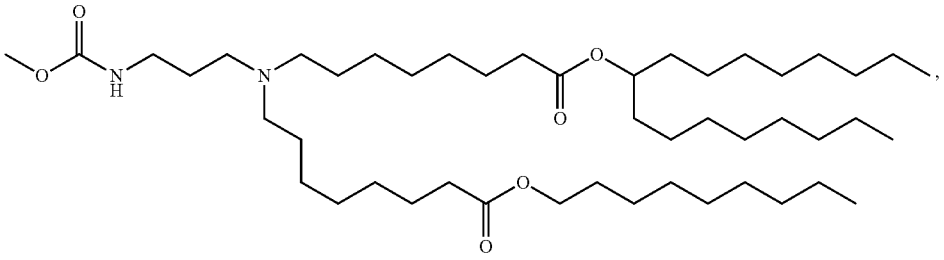

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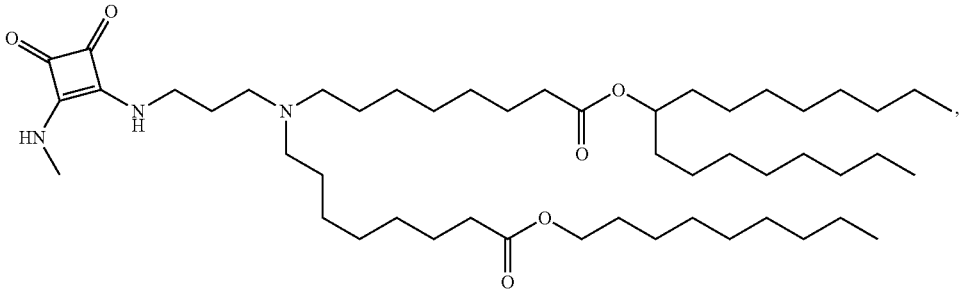

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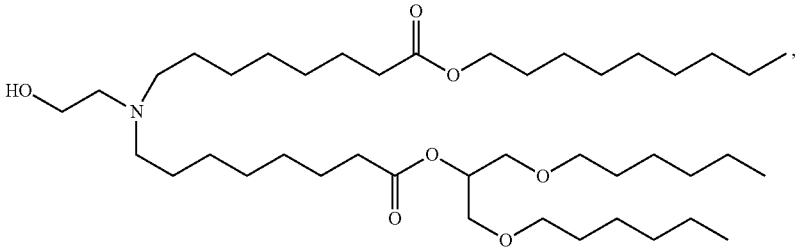

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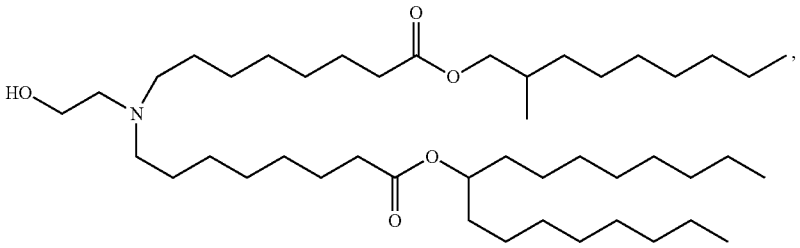

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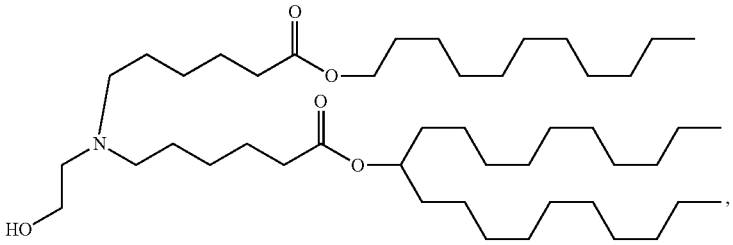

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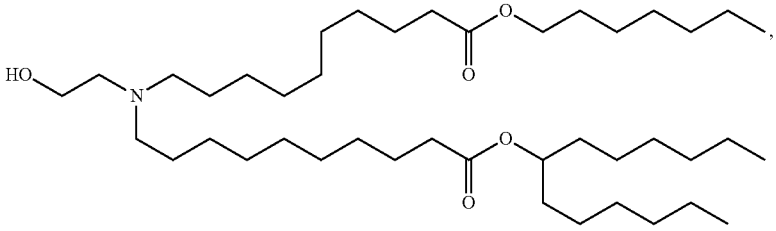

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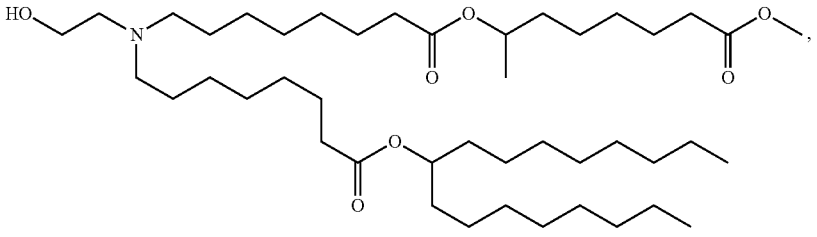

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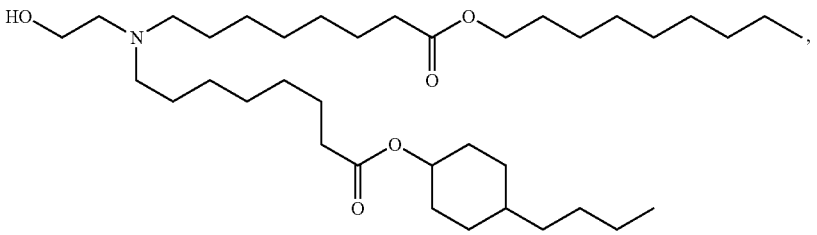
(Compound 188)



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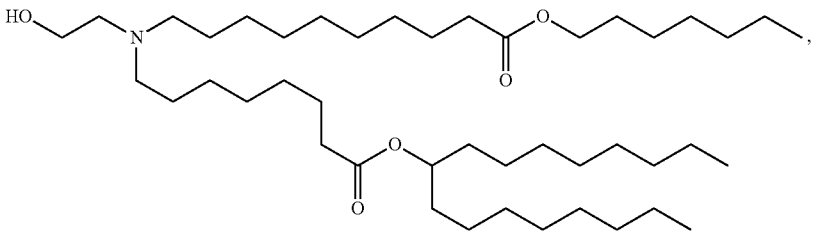

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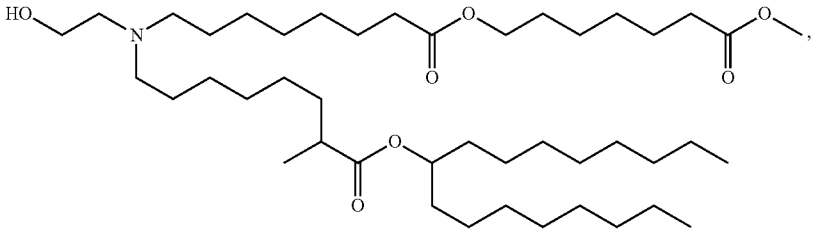

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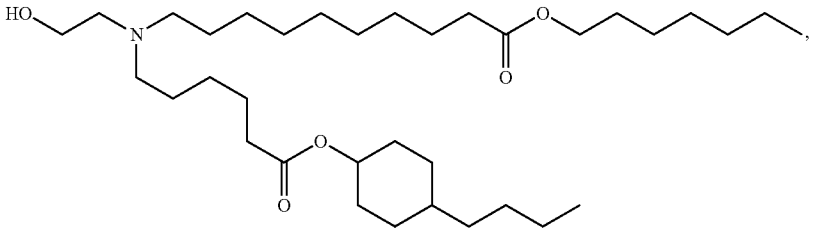

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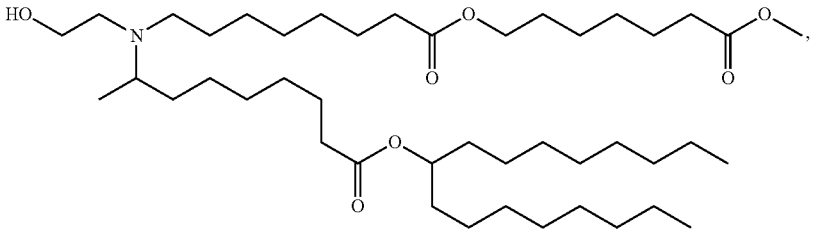

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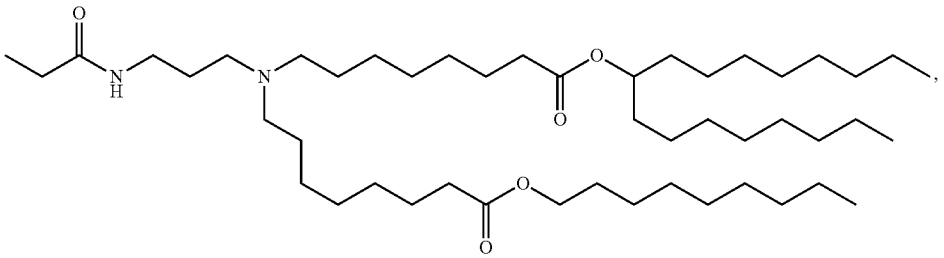

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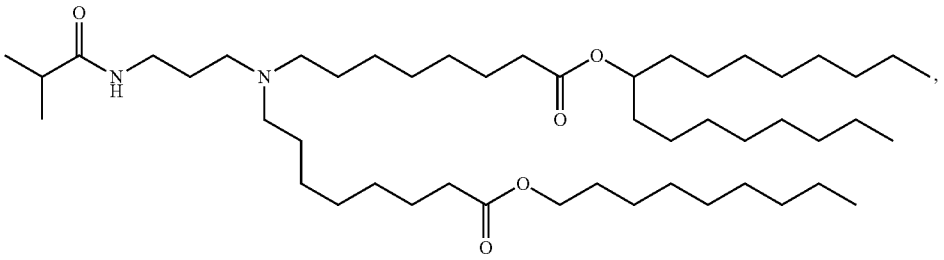

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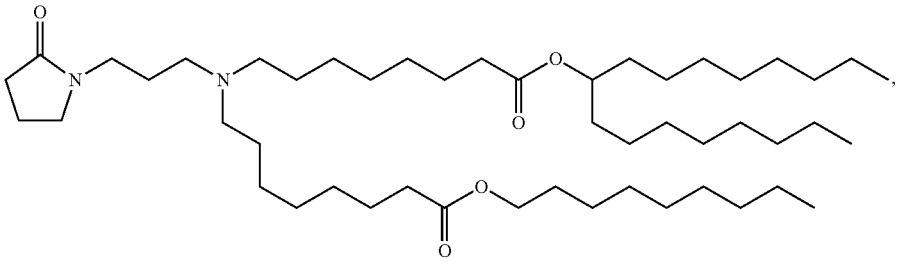

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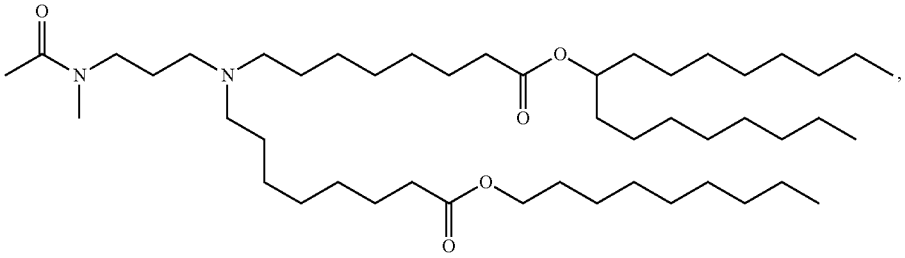

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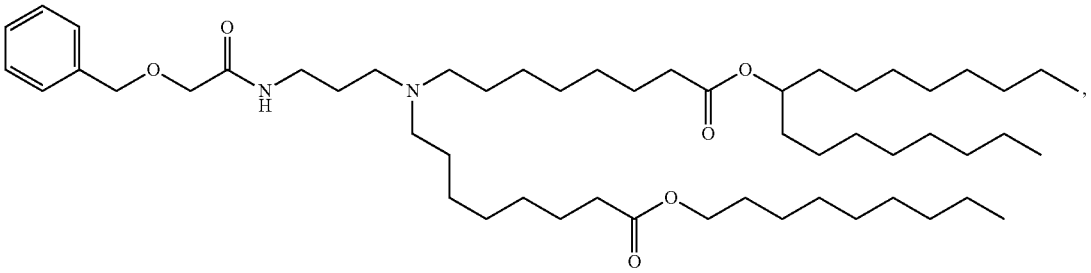

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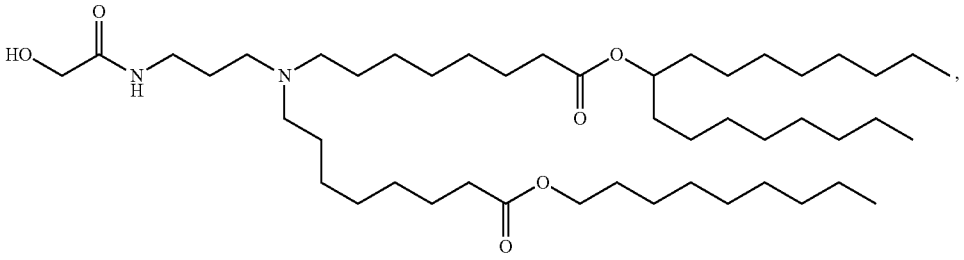

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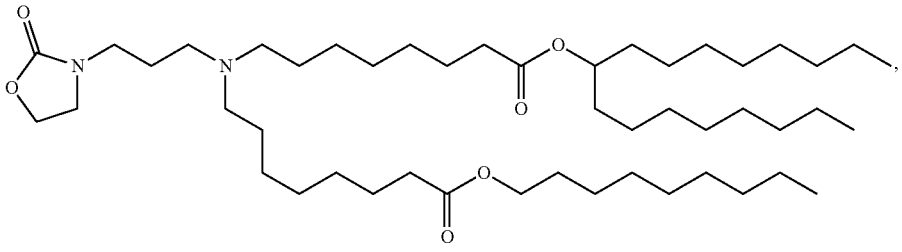

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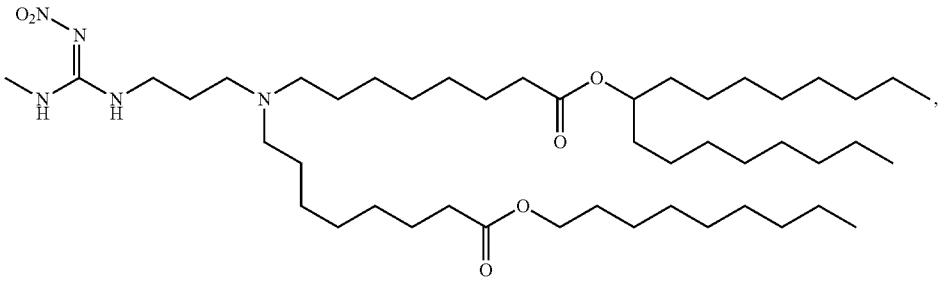

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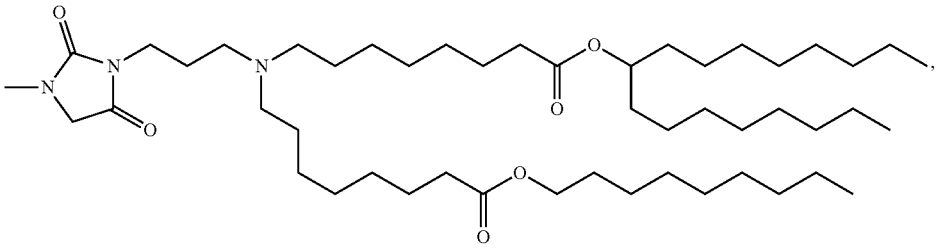
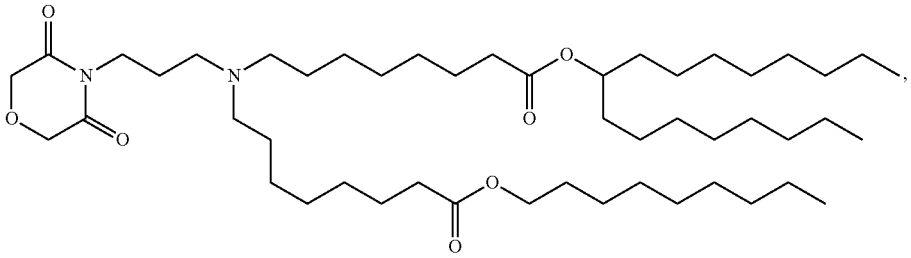
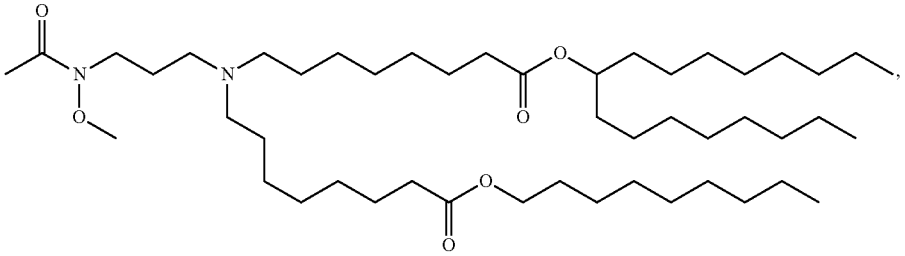


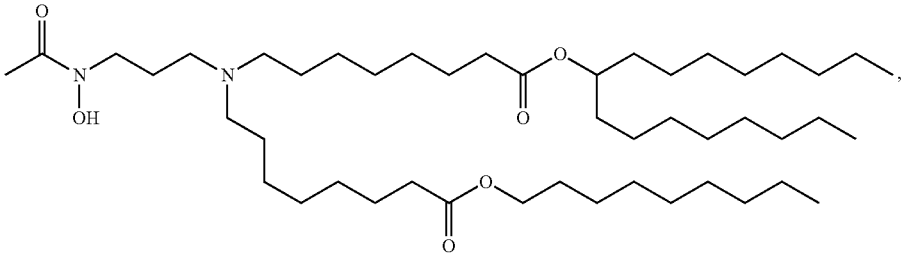
(Compound 202)



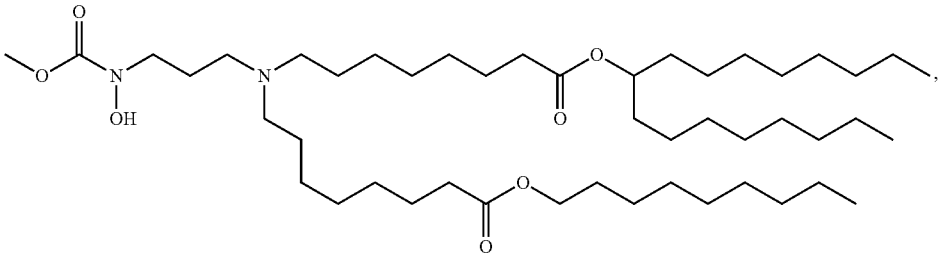
(Compound 203)



(Compound 204)



(Compound 205)



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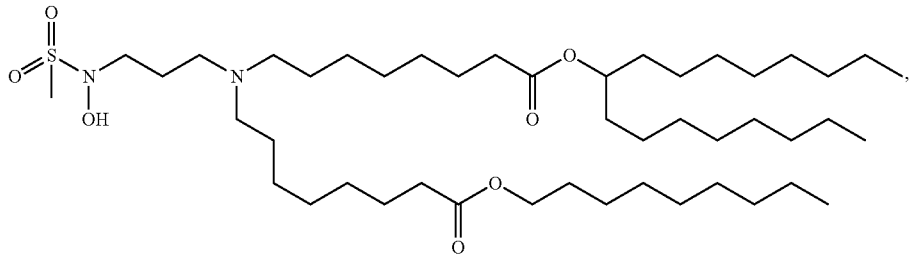
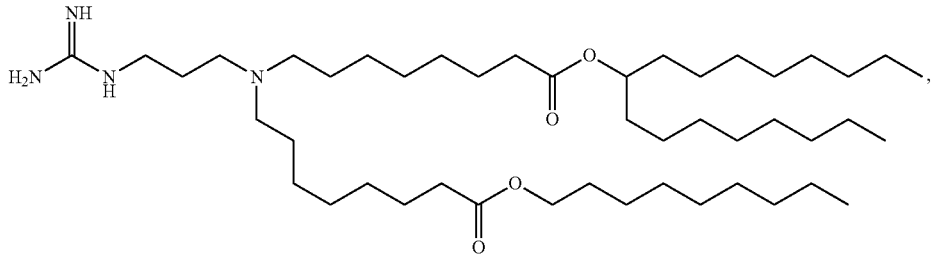
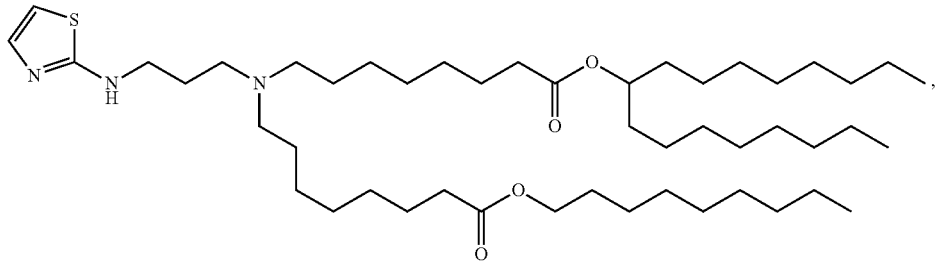
(Compound 206)



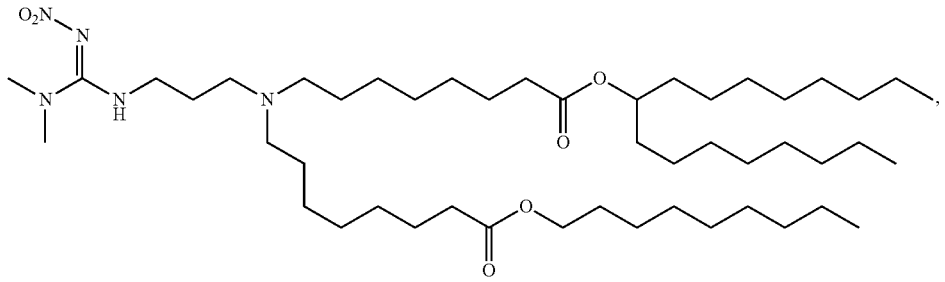
(Compound 207)



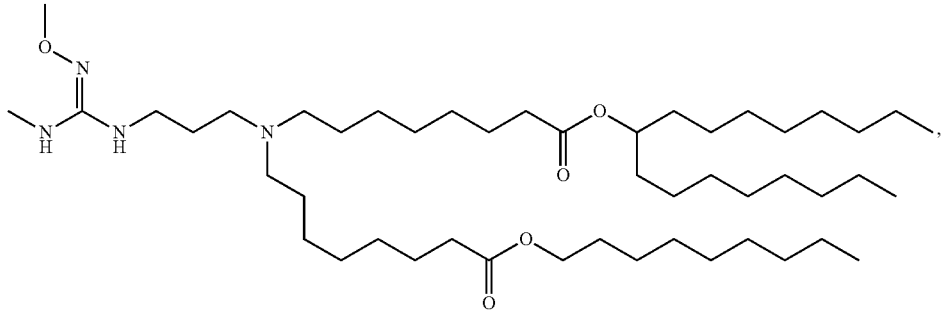
(Compound 208)



(Compound 209)



(Compound 210)



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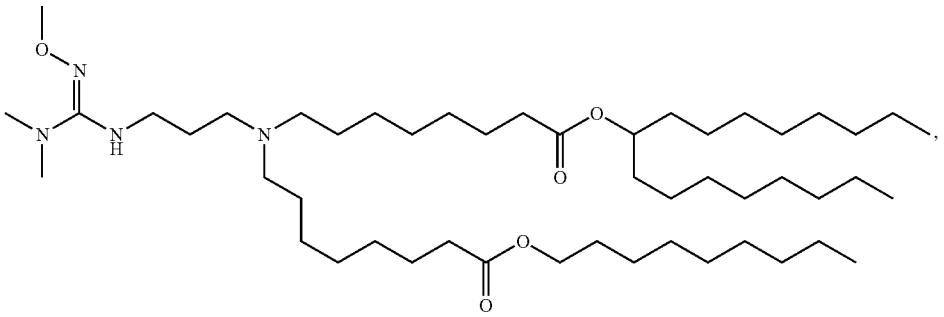
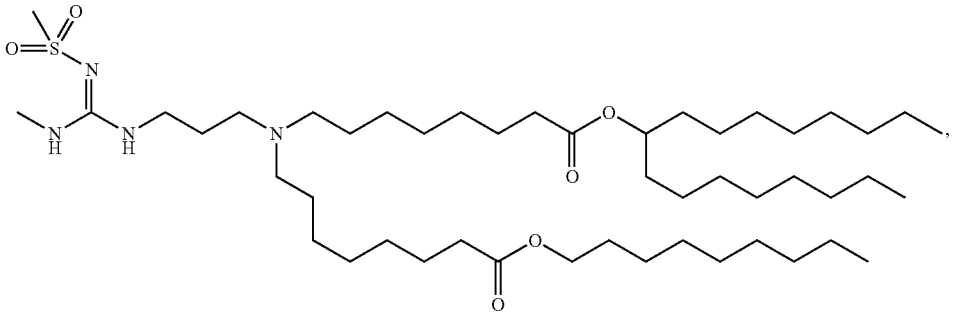
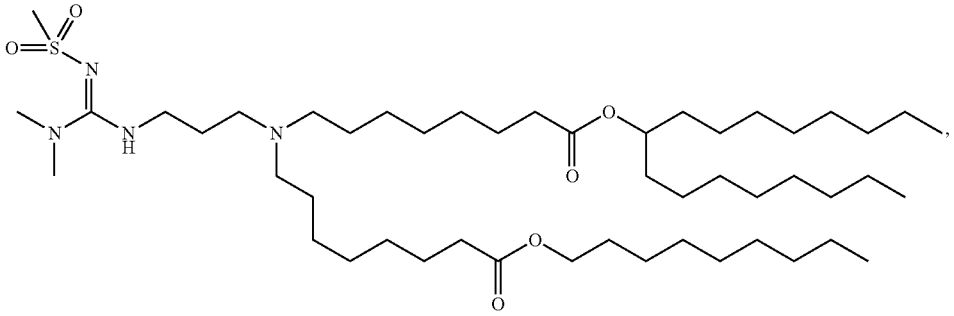
(Compound 211)



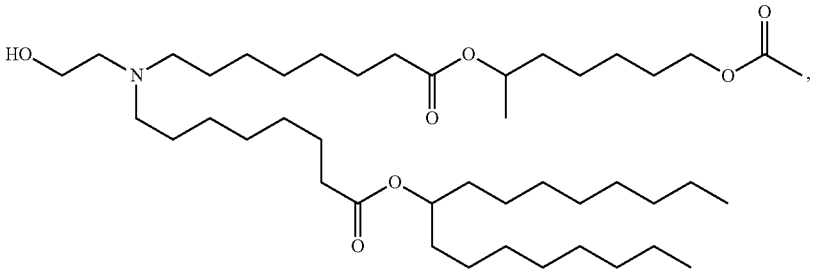
(Compound 212)



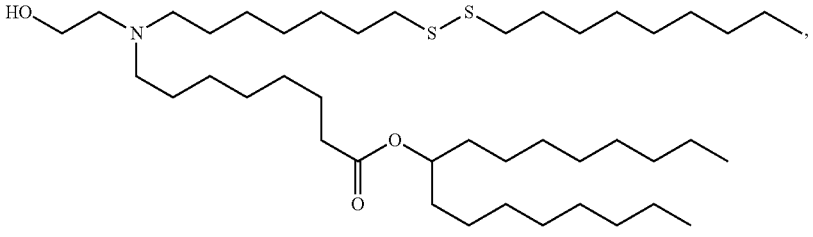
(Compound 213)



(Compound 214)



(Compound 215)



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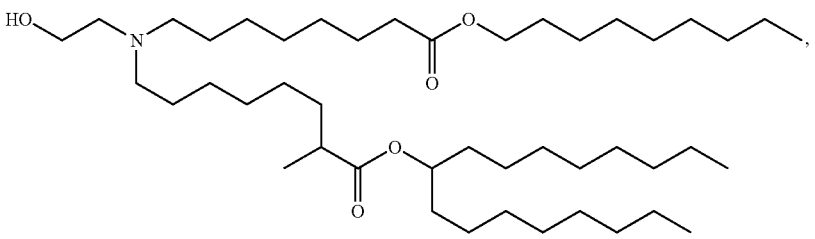
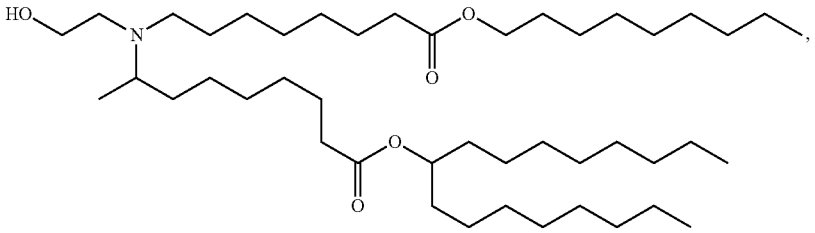
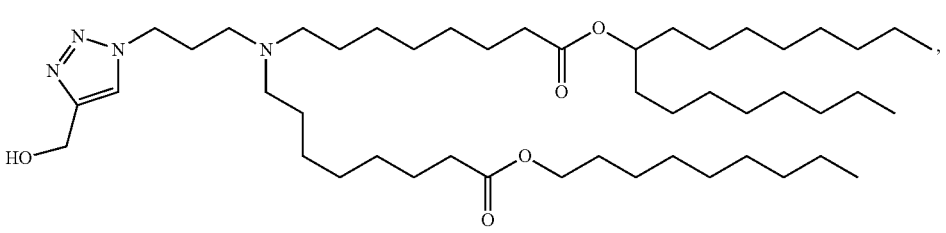
(Compound 216)



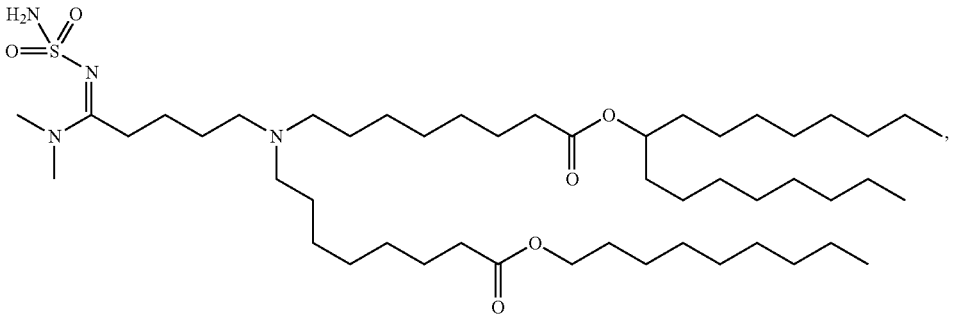
(Compound 217)



(Compound 218)



(Compound 219)



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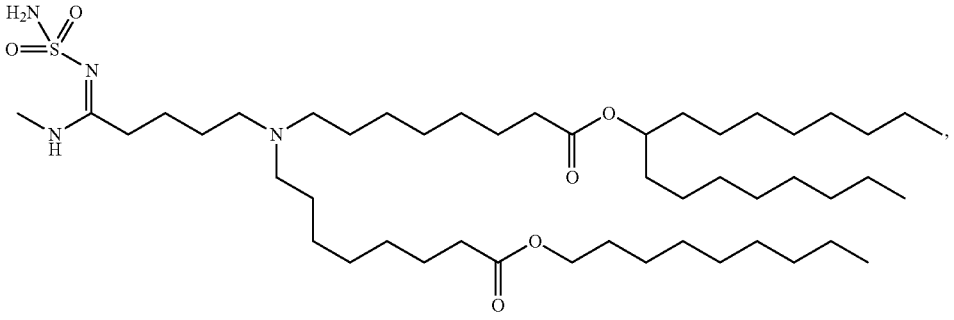

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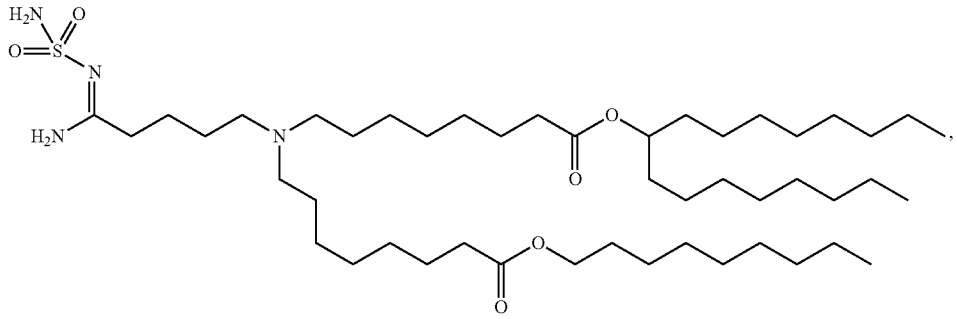
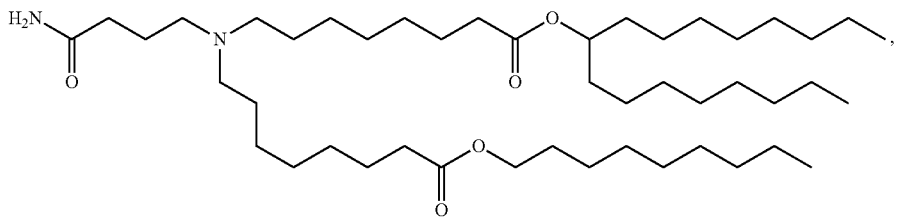
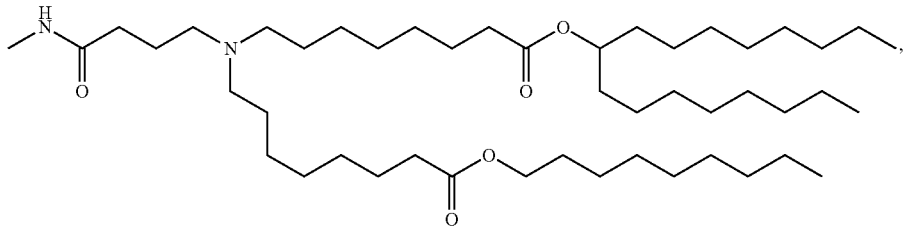
(Compound 221)



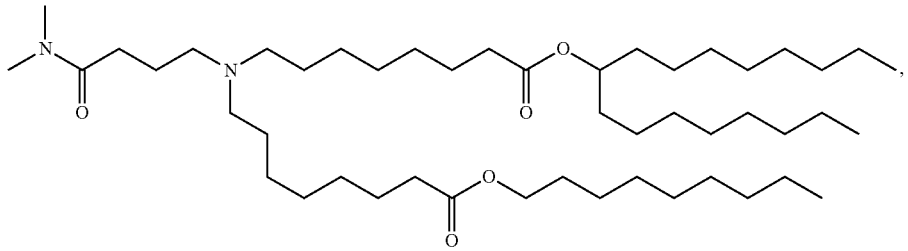
(Compound 222)



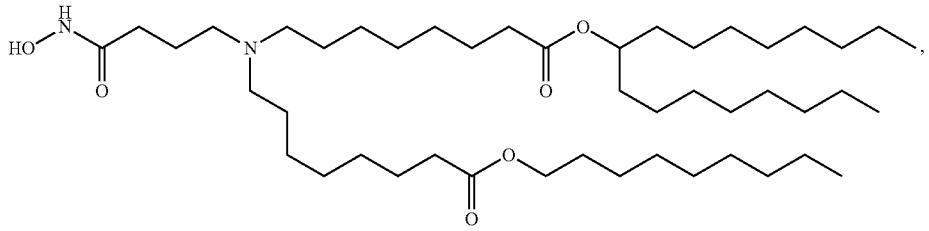
(Compound 223)



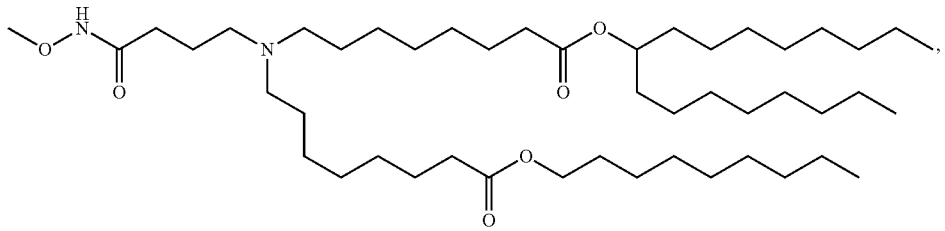
(Compound 224)



(Compound 225)



(Compound 226)



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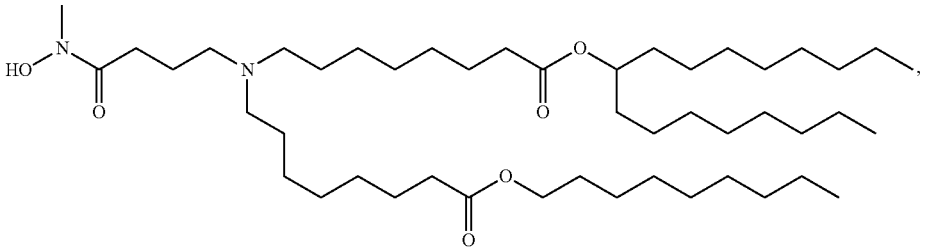
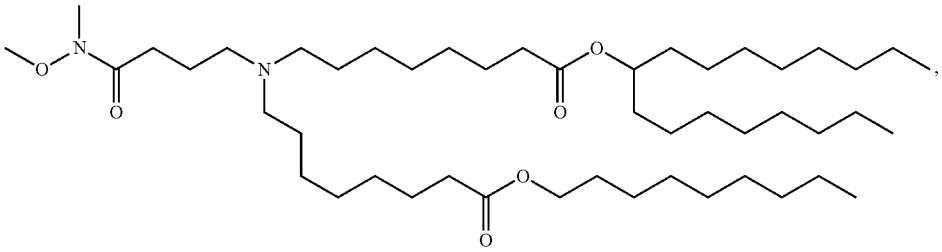
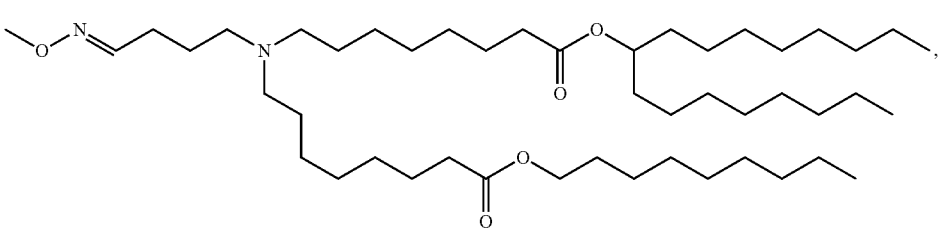
(Compound 227)



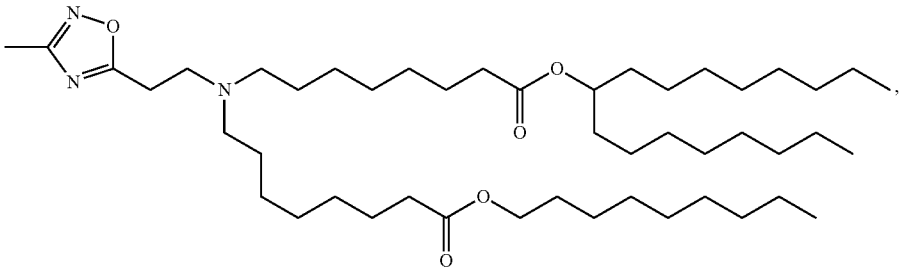
(Compound 228)



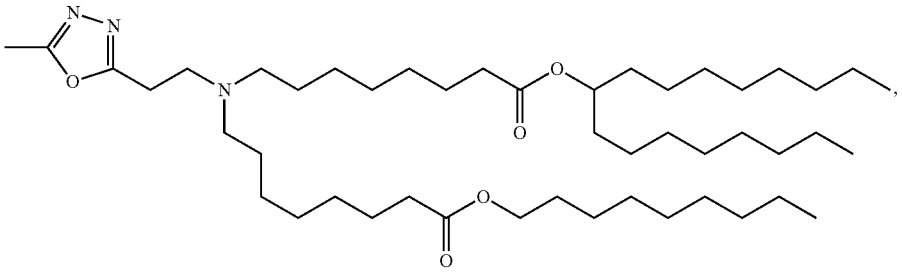
(Compound 229)



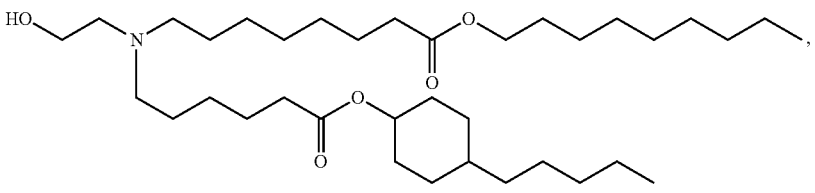
(Compound 230)



(Compound 231)



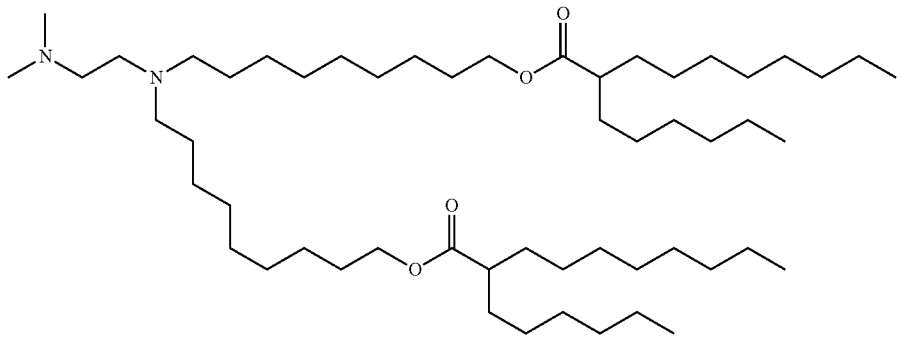
(Compound 232)



and salts and isomers thereof.

In some embodiments, a nanoparticle comprises the following compound:

(Compound 233)



or salts and isomers thereof.

In some embodiments, the disclosure features a nanoparticle composition including a lipid component comprising a compound as described herein (e.g., a compound according to Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe)).

In some embodiments, the disclosure features a pharmaceutical composition comprising a nanoparticle composition according to the preceding embodiments and a pharmaceutically acceptable carrier. For example, the pharmaceutical composition is refrigerated or frozen for storage and/or shipment (e.g., being stored at a temperature of 4° C. or lower, such as a temperature between about −150° C. and about 0° C. or between about −80° C. and about −20° C. (e.g., about −5° C., −10° C., −15° C., −20° C., −25° C., −30° C., −40° C., −50° C., −60° C., −70° C., −80° C., −90° C., −130° C. or −150° C.). For example, the pharmaceutical composition is a solution that is refrigerated for storage and/or shipment at, for example, about −20° C., −30° C., −40° C., −50° C., −60° C., −70° C., or −80° C.

In some embodiments, the disclosure provides a method of delivering a therapeutic and/or prophylactic (e.g., RNA, such as mRNA) to a cell (e.g., a mammalian cell). This method includes the step of administering to a subject (e.g., a mammal, such as a human) a nanoparticle composition including (i) a lipid component including a phospholipid (such as a polyunsaturated lipid), a PEG lipid, a structural lipid, and a compound of Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (lie) and (ii) a therapeutic and/or prophylactic, in which administering involves contacting the cell with the nanoparticle composition, whereby the therapeutic and/or prophylactic is delivered to the cell.

In some embodiments, the disclosure provides a method of producing a polypeptide of interest in a cell (e.g., a mammalian cell). The method includes the step of contacting the cell with a nanoparticle composition including (i) a lipid component including a phospholipid (such as a polyunsaturated lipid), a PEG lipid, a structural lipid, and a compound of Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe) and (ii) an mRNA encoding the polypeptide of interest, whereby the mRNA is capable of being translated in the cell to produce the polypeptide.

In some embodiments, the disclosure provides a method of treating a disease or disorder in a mammal (e.g., a human) in need thereof. The method includes the step of administering to the mammal a therapeutically effective amount of a nanoparticle composition including (i) a lipid component including a phospholipid (such as a polyunsaturated lipid), a PEG lipid, a structural lipid, and a compound of Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe) and (ii) a therapeutic and/or prophylactic (e.g., an mRNA). In some embodiments, the disease or disorder is characterized by dysfunctional or aberrant protein or polypeptide activity. For example, the disease or disorder is selected from the group consisting of rare diseases, infectious diseases, cancer and proliferative diseases, genetic diseases (e.g., cystic fibrosis), autoimmune diseases, diabetes, neurodegenerative diseases, cardio- and reno-vascular diseases, and metabolic diseases.

In some embodiments, the disclosure provides a method of delivering (e.g., specifically delivering) a therapeutic and/or prophylactic to a mammalian organ (e.g., a liver, spleen, lung, or femur). This method includes the step of administering to a subject (e.g., a mammal) a nanoparticle composition including (i) a lipid component including a phospholipid, a PEG lipid, a structural lipid, and a compound of Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe) and (ii) a therapeutic and/or prophylactic (e.g., an mRNA), in which administering involves contacting the cell with the nanoparticle composition, whereby the therapeutic and/or prophylactic is delivered to the target organ (e.g., a liver, spleen, lung, or femur).

In some embodiments, the disclosure features a method for the enhanced delivery of a therapeutic and/or prophylactic (e.g., an mRNA) to a target tissue (e.g., a liver, spleen, lung, or femur). This method includes administering to a subject (e.g., a mammal) a nanoparticle composition, the composition including (i) a lipid component including a compound of Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe), a phospholipid, a structural lipid, and a PEG lipid; and (ii) a therapeutic and/or prophylactic, the administering including contacting the target tissue with the nanoparticle composition, whereby the therapeutic and/or prophylactic is delivered to the target tissue.

In some embodiments, the disclosure features a method of lowering immunogenicity comprising introducing the nanoparticle composition of the disclosure into cells, wherein the nanoparticle composition reduces the induction of the cellular immune response of the cells to the nanoparticle composition, as compared to the induction of the cellular immune response in cells induced by a reference composition which comprises a reference lipid instead of a compound of Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe). For example, the cellular immune response is an innate immune response, an adaptive immune response, or both.

The disclosure also includes methods of synthesizing a compound of Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe) and methods of making a nanoparticle composition including a lipid component comprising the compound of Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe).

Modes of Vaccine Administration

Respiratory virus RNA (e.g. mRNA) vaccines may be administered by any route which results in a therapeutically effective outcome. These include, but are not limited, to intradermal, intramuscular, and/or subcutaneous administration. The present disclosure provides methods comprising administering RNA (e.g., mRNA) vaccines to a subject in need thereof. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the disease, the particular composition, its mode of administration, its mode of activity, and the like. Respiratory virus RNA (e.g., mRNA) vaccines compositions are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of RNA (e.g., mRNA) vaccine compositions may be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective, prophylactically effective, or appropriate imaging dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

In some embodiments, respiratory virus RNA (e.g. mRNA) vaccines compositions may be administered at dosage levels sufficient to deliver 0.0001 mg/kg to 100 mg/kg, 0.001 mg/kg to 0.05 mg/kg, 0.005 mg/kg to 0.05 mg/kg, 0.001 mg/kg to 0.005 mg/kg, 0.05 mg/kg to 0.5 mg/kg, 0.01 mg/kg to 50 mg/kg, 0.1 mg/kg to 40 mg/kg, 0.5 mg/kg to 30 mg/kg, 0.01 mg/kg to 10 mg/kg, 0.1 mg/kg to 10 mg/kg, or 1 mg/kg to 25 mg/kg, of subject body weight per day, one or more times a day, per week, per month, etc. to obtain the desired therapeutic, diagnostic, prophylactic, or imaging effect (see, e.g., the range of unit doses described in International Publication No WO2013078199, the contents of which are herein incorporated by reference in their entirety). The desired dosage may be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, every four weeks, every 2 months, every three months, every 6 months, etc. In some embodiments, the desired dosage may be delivered using multiple administrations (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations). When multiple administrations are employed, split dosing regimens such as those described herein may be used. In exemplary embodiments, respiratory virus RNA (e.g., mRNA) vaccines compositions may be administered at dosage levels sufficient to deliver 0.0005 mg/kg to 0.01 mg/kg, e.g., about 0.0005 mg/kg to about 0.0075 mg/kg, e.g., about 0.0005 mg/kg, about 0.001 mg/kg, about 0.002 mg/kg, about 0.003 mg/kg, about 0.004 mg/kg or about 0.005 mg/kg.

In some embodiments, respiratory virus RNA (e.g., mRNA) vaccine compositions may be administered once or twice (or more) at dosage levels sufficient to deliver 0.025 mg/kg to 0.250 mg/kg, 0.025 mg/kg to 0.500 mg/kg, 0.025 mg/kg to 0.750 mg/kg, or 0.025 mg/kg to 1.0 mg/kg.

In some embodiments, respiratory virus RNA (e.g., mRNA) vaccine compositions may be administered twice (e.g., Day 0 and Day 7, Day 0 and Day 14, Day 0 and Day 21, Day 0 and Day 28, Day 0 and Day 60, Day 0 and Day 90, Day 0 and Day 120, Day 0 and Day 150, Day 0 and Day 180, Day 0 and 3 months later, Day 0 and 6 months later, Day 0 and 9 months later, Day 0 and 12 months later, Day 0 and 18 months later, Day 0 and 2 years later, Day 0 and 5 years later, or Day 0 and 10 years later) at a total dose of or at dosage levels sufficient to deliver a total dose of 0.0100 mg, 0.025 mg, 0.050 mg, 0.075 mg, 0.100 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.200 mg, 0.225 mg, 0.250 mg, 0.275 mg, 0.300 mg, 0.325 mg, 0.350 mg, 0.375 mg, 0.400 mg, 0.425 mg, 0.450 mg, 0.475 mg, 0.500 mg, 0.525 mg, 0.550 mg, 0.575 mg, 0.600 mg, 0.625 mg, 0.650 mg, 0.675 mg, 0.700 mg, 0.725 mg, 0.750 mg, 0.775 mg, 0.800 mg, 0.825 mg, 0.850 mg, 0.875 mg, 0.900 mg, 0.925 mg, 0.950 mg, 0.975 mg, or 1.0 mg. Higher and lower dosages and frequency of administration are encompassed by the present disclosure. For example, a respiratory virus RNA (e.g., mRNA) vaccine composition may be administered three or four times.

In some embodiments, respiratory virus RNA (e.g., mRNA) vaccine compositions may be administered twice (e.g., Day 0 and Day 7, Day 0 and Day 14, Day 0 and Day 21, Day 0 and Day 28, Day 0 and Day 60, Day 0 and Day 90, Day 0 and Day 120, Day 0 and Day 150, Day 0 and Day 180, Day 0 and 3 months later, Day 0 and 6 months later, Day 0 and 9 months later, Day 0 and 12 months later, Day 0 and 18 months later, Day 0 and 2 years later, Day 0 and 5 years later, or Day 0 and 10 years later) at a total dose of or at dosage levels sufficient to deliver a total dose of 0.010 mg, 0.025 mg, 0.100 mg or 0.400 mg.

In some embodiments, the respiratory virus RNA (e.g., mRNA) vaccine for use in a method of vaccinating a subject is administered to the subject as a single dosage of between 10 μg/kg and 400 μg/kg of the nucleic acid vaccine (in an effective amount to vaccinate the subject). In some embodiments the RNA (e.g., mRNA) vaccine for use in a method of vaccinating a subject is administered to the subject as a single dosage of between 10 μg and 400 μg of the nucleic acid vaccine (in an effective amount to vaccinate the subject). In some embodiments, a respiratory virus RNA (e.g., mRNA) vaccine for use in a method of vaccinating a subject is administered to the subject as a single dosage of 25-1000 μg (e.g., a single dosage of mRNA encoding hMPV, PIV3, RSV, MeV and/or BetaCoV antigen). In some embodiments, a respiratory virus RNA (e.g., mRNA) vaccine is administered to the subject as a single dosage of 25, 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950 or 1000 μg. For example, a respiratory virus RNA (e.g., mRNA) vaccine may be administered to a subject as a single dose of 25-100, 25-500, 50-100, 50-500, 50-1000, 100-500, 100-1000, 250-500, 250-1000, or 500-1000 μg. In some embodiments, a respiratory virus RNA (e.g., mRNA) vaccine for use in a method of vaccinating a subject is administered to the subject as two dosages, the combination of which equals 25-1000 μg of the respiratory virus RNA (e.g., mRNA) vaccine.

A respiratory virus RNA (e.g. mRNA) vaccine pharmaceutical composition described herein can be formulated into a dosage form described herein, such as an intranasal, intratracheal, or injectable (e.g., intravenous, intraocular, intravitreal, intramuscular, intradermal, intracardiac, intraperitoneal, and subcutaneous).

Respiratory Virus RNA (e.g., mRNA) Vaccine Formulations and Methods of Use

Some aspects of the present disclosure provide formulations of the respiratory virus RNA (e.g., mRNA) vaccine, wherein the RNA (e.g., mRNA) vaccine is formulated in an effective amount to produce an antigen specific immune response in a subject (e.g., production of antibodies specific to an hMPV, PIV3, RSV, MeV and/or BetaCoV antigenic polypeptide). "An effective amount" is a dose of an RNA (e.g., mRNA) vaccine effective to produce an antigen-specific immune response. Also provided herein are methods of inducing an antigen-specific immune response in a subject.

In some embodiments, the antigen-specific immune response is characterized by measuring an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide antibody titer produced in a subject administered a respiratory virus RNA (e.g., mRNA) vaccine as provided herein. An antibody titer is a measurement of the amount of antibodies within a subject, for example, antibodies that are specific to a particular antigen (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) or epitope of an antigen. Antibody titer is typically expressed as the inverse of the greatest dilution that provides a positive result. Enzyme-linked immunosorbent assay (ELISA) is a common assay for determining antibody titers, for example.

In some embodiments, an antibody titer is used to assess whether a subject has had an infection or to determine whether immunizations are required. In some embodiments, an antibody titer is used to determine the strength of an autoimmune response, to determine whether a booster immunization is needed, to determine whether a previous vaccine was effective, and to identify any recent or prior infections. In accordance with the present disclosure, an antibody titer may be used to determine the strength of an immune response induced in a subject by the respiratory virus RNA (e.g., mRNA) vaccine.

In some embodiments, an anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a subject is increased by at least 1 log relative to a control. For example, anti-antigenic polypeptide antibody titer produced in a subject may be increased by at least 1.5, at least 2, at least 2.5, or at least 3 log relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased by 1, 1.5, 2, 2.5 or 3 log relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased by 1-3 log relative to a control. For example, the anti-antigenic polypeptide antibody titer produced in a subject may be increased by 1-1.5, 1-2, 1-2.5, 1-3, 1.5-2, 1.5-2.5, 1.5-3, 2-2.5, 2-3, or 2.5-3 log relative to a control.

In some embodiments, the anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a subject is increased at least 2 times relative to a control. For example, the anti-antigenic polypeptide antibody titer produced in a subject may be increased at least 3 times, at least 4 times, at least 5 times, at least 6 times, at least 7 times, at least 8 times, at least 9 times, or at least 10 times relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased 2, 3, 4, 5, 6, 7, 8, 9, or 10 times relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in a subject is increased 2-10 times relative to a control. For example, the anti-antigenic polypeptide antibody titer produced in a subject may be increased 2-10, 2-9, 2-8, 2-7, 2-6, 2-5, 2-4, 2-3, 3-10, 3-9, 3-8, 3-7, 3-6, 3-5, 3-4, 4-10, 4-9, 4-8, 4-7, 4-6, 4-5, 5-10, 5-9, 5-8, 5-7, 5-6, 6-10, 6-9, 6-8, 6-7, 7-10, 7-9, 7-8, 8-10, 8-9, or 9-10 times relative to a control.

A control, in some embodiments, is the anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a subject who has not been administered a respiratory virus RNA (e.g., mRNA) vaccine of the present disclosure. In some embodiments, a control is an anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a subject who has been administered a live attenuated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine. An attenuated vaccine is a vaccine produced by reducing the virulence of a viable (live). An attenuated virus is altered in a manner that renders it harmless or less virulent relative to live, unmodified virus. In some embodiments, a control is an anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a subject administered inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine. In some embodiments, a control is an anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a subject administered a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine. Recombinant protein vaccines typically include protein antigens that either have been produced in a heterologous expression system (e.g., bacteria or yeast) or purified from large amounts of the pathogenic organism. In some embodiments, a control is an anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a subject who has been administered an hMPV, PIV3, RSV, MeV and/or BetaCoV virus-like particle (VLP) vaccine. For example, an hMPV VLP vaccine used as a control may be a hMPV VLPs, comprising (or consisting of) viral matrix (M) and fusion (F) proteins, generated by expressing viral proteins in suspension-adapted human embryonic kidney epithelial (293-F) cells (see, e.g., Cox R G et al., *J Virol.* 2014 June; 88(11): 6368-6379, the contents of which are herein incorporated by reference).

In some embodiments, an effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a dose that is reduced compared to the standard of care dose of a recombinant hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine. A "standard of care," as provided herein, refers to a medical or psychological treatment guideline and can be general or specific. "Standard of care" specifies appropriate treatment based on scientific evidence and collaboration between medical professionals involved in the treatment of a given condition. It is the diagnostic and treatment process that a physician/clinician should follow for a certain type of patient, illness or clinical circumstance. A "standard of care dose," as provided herein, refers to the dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine, or a live attenuated or inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine, that a physician/clinician or other medical professional would administer to a subject to treat or prevent hMPV, PIV3, RSV, MeV and/or BetaCoV, or a hMPV-, PIV3-, RSV-, MeV- and/or BetaCoV-related condition, while following the standard of care

guideline for treating or preventing hMPV, PIV3, RSV, MeV and/or BetaCoV, or a hMPV-, PIV3-, RSV-, MeV- and/or BetaCoV-related condition.

In some embodiments, the anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a subject administered an effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is equivalent to an anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a control subject administered a standard of care dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine or a live attenuated or inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine.

In some embodiments, an effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a dose equivalent to an at least 2-fold reduction in a standard of care dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine. For example, an effective amount of a respiratory virus RNA (e.g., mRNA) vaccine may be a dose equivalent to an at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, or at least 10-fold reduction in a standard of care dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine. In some embodiments, an effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a dose equivalent to an at least at least 100-fold, at least 500-fold, or at least 1000-fold reduction in a standard of care dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine. In some embodiments, an effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a dose equivalent to a 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 20-, 50-, 100-, 250-, 500-, or 1000-fold reduction in a standard of care dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine. In some embodiments, the anti-antigenic polypeptide antibody titer produced in a subject administered an effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant or protein hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine or a live attenuated or inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine. In some embodiments, an effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a dose equivalent to a 2-fold to 1000-fold (e.g., 2-fold to 100-fold, 10-fold to 1000-fold) reduction in the standard of care dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine, wherein the anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine or a live attenuated or inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine.

In some embodiments, the effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a dose equivalent to a 2 to 1000-, 2 to 900-, 2 to 800-, 2 to 700-, 2 to 600-, 2 to 500-, 2 to 400-, 2 to 300-, 2 to 200-, 2 to 100-, 2 to 90-, 2 to 80-, 2 to 70-, 2 to 60-, 2 to 50-, 2 to 40-, 2 to 30-, 2 to 20-, 2 to 10-, 2 to 9-, 2 to 8-, 2 to 7-, 2 to 6-, 2 to 5-, 2 to 4-, 2 to 3-, 3 to 1000-, 3 to 900-, 3 to 800-, 3 to 700-, 3 to 600-, 3 to 500-, 3 to 400-, 3 to 3 to 00-, 3 to 200-, 3 to 100-, 3 to 90-, 3 to 80-, 3 to 70-, 3 to 60-, 3 to 50-, 3 to 40-, 3 to 30-, 3 to 20-, 3 to 10-, 3 to 9-, 3 to 8-, 3 to 7-, 3 to 6-, 3 to 5-, 3 to 4-, 4 to 1000-, 4 to 900-, 4 to 800-, 4 to 700-, 4 to 600-, 4 to 500-, 4 to 400-, 4 to 4 to 00-, 4 to 200-, 4 to 100-, 4 to 90-, 4 to 80-, 4 to 70-, 4 to 60-, 4 to 50-, 4 to 40-, 4 to 30-, 4 to 20-, 4 to 10-, 4 to 9-, 4 to 8-, 4 to 7-, 4 to 6-, 4 to 5-, 4 to 4-, 5 to 1000-, 5 to 900-, 5 to 800-, 5 to 700-, 5 to 600-, 5 to 500-, 5 to 400-, 5 to 300-, 5 to 200-, 5 to 100-, 5 to 90-, 5 to 80-, 5 to 70-, 5 to 60-, 5 to 50-, 5 to 40-, 5 to 30-, 5 to 20-, 5 to 10-, 5 to 9-, 5 to 8-, 5 to 7-, 5 to 6-, 6 to 1000-, 6 to 900-, 6 to 800-, 6 to 700-, 6 to 600-, 6 to 500-, 6 to 400-, 6 to 300-, 6 to 200-, 6 to 100-, 6 to 90-, 6 to 80-, 6 to 70-, 6 to 60-, 6 to 50-, 6 to 40-, 6 to 30-, 6 to 20-, 6 to 10-, 6 to 9-, 6 to 8-, 6 to 7-, 7 to 1000-, 7 to 900-, 7 to 800-, 7 to 700-, 7 to 600-, 7 to 500-, 7 to 400-, 7 to 300-, 7 to 200-, 7 to 100-, 7 to 90-, 7 to 80-, 7 to 70-, 7 to 60-, 7 to 50-, 7 to 40-, 7 to 30-, 7 to 20-, 7 to 10-, 7 to 9-, 7 to 8-, 8 to 1000-, 8 to 900-, 8 to 800-, 8 to 700-, 8 to 600-, 8 to 500-, 8 to 400-, 8 to 300-, 8 to 200-, 8 to 100-, 8 to 90-, 8 to 80-, 8 to 70-, 8 to 60-, 8 to 50-, 8 to 40-, 8 to 30-, 8 to 20-, 8 to 10-, 8 to 9-, 9 to 1000-, 9 to 900-, 9 to 800-, 9 to 700-, 9 to 600-, 9 to 500-, 9 to 400-, 9 to 300-, 9 to 200-, 9 to 100-, 9 to 90-, 9 to 80-, 9 to 70-, 9 to 60-, 9 to 50-, 9 to 40-, 9 to 30-, 9 to 20-, 9 to 10-, 10 to 1000-, 10 to 900-, 10 to 800-, 10 to 700-, 10 to 600-, 10 to 500-, 10 to 400-, 10 to 300-, 10 to 200-, 10 to 100-, 10 to 90-, 10 to 80-, 10 to 70-, 10 to 60-, 10 to 50-, 10 to 40-, 10 to 30-, 10 to 20-, 20 to 1000-, 20 to 900-, 20 to 800-, 20 to 700-, 20 to 600-, 20 to 500-, 20 to 400-, 20 to 300-, 20 to 200-, 20 to 100-, 20 to 90-, 20 to 80-, 20 to 70-, 20 to 60-, 20 to 50-, 20 to 40-, 20 to 30-, 30 to 1000-, 30 to 900-, 30 to 800-, 30 to 700-, 30 to 600-, 30 to 500-, 30 to 400-, 30 to 300-, 30 to 200-, 30 to 100-, 30 to 90-, 30 to 80-, 30 to 70-, 30 to 60-, 30 to 50-, 30 to 40-, 40 to 1000-, 40 to 900-, 40 to 800-, 40 to 700-, 40 to 600-, 40 to 500-, 40 to 400-, 40 to 300-, 40 to 200-, 40 to 100-, 40 to 90-, 40 to 80-, 40 to 70-, 40 to 60-, 40 to 50-, 50 to 1000-, 50 to 900-, 50 to 800-, 50 to 700-, 50 to 600-, 50 to 500-, 50 to 400-, 50 to 300-, 50 to 200-, 50 to 100-, 50 to 90-, 50 to 80-, 50 to 70-, 50 to 60-, 60 to 1000-, 60 to 900-, 60 to 800-, 60 to 700-, 60 to 600-, 60 to 500-, 60 to 400-, 60 to 300-, 60 to 200-, 60 to 100-, 60 to 90-, 60 to 80-, 60 to 70-, 70 to 1000-, 70 to 900-, 70 to 800-, 70 to 700-, 70 to 600-, 70 to 500-, 70 to 400-, 70 to 300-, 70 to 200-, 70 to 100-, 70 to 90-, 70 to 80-, 80 to 1000-, 80 to 900-, 80 to 800-, 80 to 700-, 80 to 600-, 80 to 500-, 80 to 400-, 80 to 300-, 80 to 200-, 80 to 100-, 80 to 90-, 90 to 1000-, 90 to 900-, 90 to 800-, 90 to 700-, 90 to 600-, 90 to 500-, 90 to 400-, 90 to 300-, 90 to 200-, 90 to 100-, 100 to 1000-, 100 to 900-, 100 to 800-, 100 to 700-, 100 to 600-, 100 to 500-, 100 to 400-, 100 to 300-, 100 to 200-, 200 to 1000-, 200 to 900-, 200 to 800-, 200 to 700-, 200 to 600-, 200 to 500-, 200 to 400-, 200 to 300-, 300 to 1000-, 300 to 900-, 300 to 800-, 300 to 700-, 300 to 600-, 300 to 500-, 300 to 400-, 400 to 1000-, 400 to 900-, 400 to 800-, 400 to 700-, 400 to 600-, 400 to 500-, 500 to 1000-, 500 to 900-, 500 to 800-, 500 to 700-, 500 to 600-, 600 to 1000-, 600 to 900-, 600 to 800-, 600 to 700-, 700 to 1000-, 700 to 900-, 700 to 800-, 800 to 1000-, 800 to 900-, or 900 to 1000-fold reduction in the standard of care dose of a recombinant hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine or a live attenuated or inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine. In some embodiments, the effective amount is a dose equivalent to (or equivalent to an at least) 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 20-, 30-, 40-, 50-, 60-, 70-, 80-, 90-, 100-, 110-, 120-, 130-,

140-, 150-, 160-, 170-, 1280-, 190-, 200-, 210-, 220-, 230-, 240-, 250-, 260-, 270-, 280-, 290-, 300-, 310-, 320-, 330-, 340-, 350-, 360-, 370-, 380-, 390-, 400-, 410-, 420-, 430-, 440-, 450-, 4360-, 470-, 480-, 490-, 500-, 510-, 520-, 530-, 540-, 550-, 560-, 5760-, 580-, 590-, 600-, 610-, 620-, 630-, 640-, 650-, 660-, 670-, 680-, 690-, 700-, 710-, 720-, 730-, 740-, 750-, 760-, 770-, 780-, 790-, 800-, 810-, 820-, 830-, 840-, 850-, 860-, 870-, 880-, 890-, 900-, 910-, 920-, 930-, 940-, 950-, 960-, 970-, 980-, 990-, or 1000-fold reduction in the standard of care dose of a recombinant hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine. In some embodiments, an anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine or a live attenuated or inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine.

In some embodiments, the effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a total dose of 50-1000 μg. In some embodiments, the effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a total dose of 50-1000, 50-900, 50-800, 50-700, 50-600, 50-500, 50-400, 50-300, 50-200, 50-100, 50-90, 50-80, 50-70, 50-60, 60-1000, 60-900, 60-800, 60-700, 60-600, 60-500, 60-400, 60-300, 60-200, 60-100, 60-90, 60-80, 60-70, 70-1000, 70-900, 70-800, 70-700, 70-600, 70-500, 70-400, 70-300, 70-200, 70-100, 70-90, 70-80, 80-1000, 80-900, 80-800, 80-700, 80-600, 80-500, 80-400, 80-300, 80-200, 80-100, 80-90, 90-1000, 90-900, 90-800, 90-700, 90-600, 90-500, 90-400, 90-300, 90-200, 90-100, 100-1000, 100-900, 100-800, 100-700, 100-600, 100-500, 100-400, 100-300, 100-200, 200-1000, 200-900, 200-800, 200-700, 200-600, 200-500, 200-400, 200-300, 300-1000, 300-900, 300-800, 300-700, 300-600, 300-500, 300-400, 400-1000, 400-900, 400-800, 400-700, 400-600, 400-500, 500-1000, 500-900, 500-800, 500-700, 500-600, 600-1000, 600-900, 600-900, 600-700, 700-1000, 700-900, 700-800, 800-1000, 800-900, or 900-1000 μg. In some embodiments, the effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a total dose of 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950 or 1000 μg. In some embodiments, the effective amount is a dose of 25-500 μg administered to the subject a total of two times. In some embodiments, the effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a dose of 25-500, 25-400, 25-300, 25-200, 25-100, 25-50, 50-500, 50-400, 50-300, 50-200, 50-100, 100-500, 100-400, 100-300, 100-200, 150-500, 150-400, 150-300, 150-200, 200-500, 200-400, 200-300, 250-500, 250-400, 250-300, 300-500, 300-400, 350-500, 350-400, 400-500 or 450-500 μg administered to the subject a total of two times. In some embodiments, the effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a total dose of 25, 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 μg administered to the subject a total of two times.

Examples of Additional Embodiments of the Disclosure

Additional embodiments of the present disclosure are encompassed by the following numbered paragraphs:

1. A respiratory virus vaccine, comprising: at least one ribonucleic acid (RNA) polynucleotide having an open reading frame encoding at least one, at least two, at least three, at least four or at least five antigenic polypeptides selected from human *Metapneumovirus* (hMPV) antigenic polypeptides or immunogenic fragments thereof, human parainfluenza virus type 3 (PIV3) antigenic polypeptides or immunogenic fragments thereof, respiratory syncytial virus (RSV) antigenic polypeptides or immunogenic fragments thereof, measles virus (MeV) antigenic polypeptides or immunogenic fragments thereof, and *Betacoronavirus* (BetaCoV) antigenic polypeptides or immunogenic fragments thereof.

2. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof and a PIV3 antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof.

3. The respiratory virus vaccine of paragraph 2, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, and/or wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13.

4. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof and a RSV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof.

5. The respiratory virus vaccine of paragraph 4, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8.

6. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof and MeV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof.

7. The respiratory virus vaccine of paragraph 6, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, and/or wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50.

8. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immu-

nogenic fragment thereof and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

9. The respiratory virus vaccine of paragraph 8, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34.

10. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof and a RSV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof.

11. The respiratory virus vaccine of paragraph 10, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13.

12. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof and a MeV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof.

13. The respiratory virus vaccine of paragraph 12, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, and/or wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50.

14. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof and a BetaCoV antigenic

polypeptide or an immunogenic fragment thereof; or at least two RNA polynucleotides, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

15. The respiratory virus vaccine of paragraph 14, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34.

16. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof and a MeV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof.

17. The respiratory virus vaccine of paragraph 16, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50.

18. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

19. The respiratory virus vaccine of paragraph 18, wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34.

20. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

21. The respiratory virus vaccine of paragraph 20, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34.

22. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a PIV3 antigenic polypeptide or an immunogenic fragment thereof, and a RSV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof.

23. The respiratory virus vaccine of paragraph 22, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, and/or wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13.

24. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a PIV3 antigenic polypeptide or an immunogenic fragment thereof, and a MeV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof.

25. The respiratory virus vaccine of paragraph 24, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, and/or wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50.

26. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a PIV3 antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

27. The respiratory virus vaccine of paragraph 26, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13 and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 23-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 23-34.

28. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, and a MeV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof.

29. The respiratory virus vaccine of paragraph 28, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, and/or wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50.

30. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

31. The respiratory virus vaccine of paragraph 30, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 23-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 23-34.

32. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a MeV antigenic polypeptide or

an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

33. The respiratory virus vaccine of paragraph 32, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 23-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 23-34.

34. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, and a MeV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof.

35. The respiratory virus vaccine of paragraph 34, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, and/or wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50.

36. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

37. The respiratory virus vaccine of paragraph 36, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 23-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 23-34.

38. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, a MeV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

39. The respiratory virus vaccine of paragraph 38, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 23-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 23-34.

40. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, a MeV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

41. The respiratory virus vaccine of paragraph 40, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 23-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 23-34.

42. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a PIV3 antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, and a MeV antigenic polypeptide or an immunogenic fragment thereof; or

at least two, three or four RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic

polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof.

43. The respiratory virus vaccine of paragraph 42, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, and/or wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50.

44. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a PIV3 antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two, three or four RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

45. The respiratory virus vaccine of paragraph 44, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34.

46. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a PIV3 antigenic polypeptide or an immunogenic fragment thereof, a MeV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two, three or four RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

47. The respiratory virus vaccine of paragraph 46, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34.

48. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, a MeV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two, three or four RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

49. The respiratory virus vaccine of paragraph 48, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34.

50. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, a MeV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two, three or four RNA polynucleotides, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, one hav-

ing an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

51. The respiratory virus vaccine of paragraph 50, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34.

52. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a PIV3 antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, a MeV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two, three, four or five RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

53. The respiratory virus vaccine of paragraph 52, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34.

54. The vaccine of any one of paragraphs 1-53, wherein at least one RNA polynucleotide has less than 80% identity to wild-type mRNA sequence.

55. The vaccine of any one of paragraphs 1-53, wherein at least one RNA polynucleotide has at least 80% identity to wild-type mRNA sequence, but does not include wild-type mRNA sequence.

56. The vaccine of any one of paragraphs 1-55, wherein at least one antigenic polypeptide has membrane fusion activity, attaches to cell receptors, causes fusion of viral and cellular membranes, and/or is responsible for binding of the virus to a cell being infected.

57. The vaccine of any one of paragraphs 1-56, wherein at least one RNA polynucleotide comprises at least one chemical modification.

58. The vaccine of paragraph 57, wherein the chemical modification is selected from pseudouridine, N1-methylpseudouridine, N1-ethylpseudouridine, 2-thiouridine, 4'-thiouridine, 5-methylcytosine, 5-methyluridine, 2-thio-1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-pseudouridine, 2-thio-5-aza-uridine, 2-thio-dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-pseudouridine, 4-methoxy-2-thio-pseudouridine, 4-methoxy-pseudouridine, 4-thio-1-methyl-pseudouridine, 4-thio-pseudouridine, 5-aza-uridine, dihydropseudouridine, 5-methoxyuridine and 2'-O-methyl uridine.

59. The vaccine of paragraph 57 or 58, wherein the chemical modification is in the 5-position of the uracil.

60. The vaccine of any one of paragraphs 57-59, wherein the chemical modification is a N1-methylpseudouridine or N1-ethylpseudouridine.

61. The vaccine of any one of paragraphs 57-60, wherein at least 80%, at least 90% or 100% of the uracil in the open reading frame have a chemical modification.

62. The vaccine of any one of paragraphs 1-61, wherein at least one RNA polynucleotide further encodes at least one 5' terminal cap, optionally wherein the 5' terminal cap is 7mG(5')ppp(5')NlmpNp.

63. The vaccine of any one of paragraphs 1-62, wherein at least one antigenic polypeptide or immunogenic fragment thereof is fused to a signal peptide selected from: a HuIgGk signal peptide (METPAQLLFLLLLWLPDTTG; SEQ ID NO: 15); IgE heavy chain epsilon-1 signal peptide (MDWTWILFLVAAATRVHS; SEQ ID NO: 16); Japanese encephalitis PRM signal sequence (MLGSNSGQRVVFTILLLLVAPAYS; SEQ ID NO: 17), VSVg protein signal sequence (MKCLLYLAFLFIGVNCA; SEQ ID NO: 18) and Japanese encephalitis JEV signal sequence (MWLVSLAIVTACAGA; SEQ ID NO:19).

64. The vaccine of paragraph 63, wherein the signal peptide is fused to the N-terminus or the C-terminus of at least one antigenic polypeptide.

65. The vaccine of any one of paragraphs 1-64, wherein the antigenic polypeptide or immunogenic fragment thereof comprises a mutated N-linked glycosylation site.

66. The vaccine of any one of paragraphs 1-65 formulated in a nanoparticle, optionally a lipid nanoparticle.

67. The vaccine of paragraph 66, wherein the lipid nanoparticle comprises a cationic lipid, a PEG-modified lipid, a sterol and a non-cationic lipid; optionally wherein the lipid nanoparticle carrier comprises a molar ratio of about 20-60% cationic lipid, 0.5-15% PEG-modified lipid, 25-55% sterol, and 25% non-cationic lipid; optionally wherein the cationic lipid is an ionizable cationic lipid and the non-cationic lipid is a neutral lipid, and the sterol is a cholesterol; and optionally wherein the cationic lipid is selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319). Formula (II)

68. The vaccine of paragraph 66 or 67, wherein the nanoparticle (e.g., lipid nanoparticle) comprises a compound of

Formula (I) and/or Formula (II), optionally Compound 3, 18, 20, 25, 26, 29, 30, 60, 108-112, or 122.

69. The vaccine of any one of paragraphs 1-68 further comprising an adjuvant, optionally a flagellin protein or peptide that optionally comprises an amino acid sequence identified by any one of SEQ ID NO: 54-56.

70. The vaccine of any one of paragraphs 1-69, wherein the open reading frame is codon-optimized.

71. The vaccine of any one of paragraphs 1-70 formulated in an effective amount to produce an antigen-specific immune response.

72. A method of inducing an immune response in a subject, the method comprising administering to the subject the vaccine of any one of paragraphs 1-71 in an amount effective to produce an antigen-specific immune response in the subject.

73. The method of paragraph 72, wherein the subject is administered a single dose of the vaccine, or wherein the subject is administered a first dose and then a booster dose of the vaccine.

74. The method of paragraph 72 or 73, wherein the vaccine is administered to the subject by intradermal injection or intramuscular injection.

75. The method of any one of paragraphs 72-74, wherein an anti-antigenic polypeptide antibody titer produced in the subject is increased by at least 1 log relative to a control, and/or wherein the anti-antigenic polypeptide antibody titer produced in the subject is increased at least 2 times relative to a control.

76. The method of any one of paragraphs 72-75, wherein the control is an anti-antigenic polypeptide antibody titer produced in a subject who has not been administered a vaccine against the virus, and/or wherein the control is an anti-antigenic polypeptide antibody titer produced in a subject who has been administered a live attenuated vaccine or an inactivated vaccine against the virus, and/or, wherein the control is an anti-antigenic polypeptide antibody titer produced in a subject who has been administered a recombinant protein vaccine or purified protein vaccine against the virus, and/or wherein the control is an anti-antigenic polypeptide antibody titer produced in a subject who has been administered a VLP vaccine against the virus.

77. The method of any one of paragraphs 72-76, wherein the effective amount is a dose equivalent to an at least 2-fold reduction in the standard of care dose of a recombinant protein vaccine or a purified protein vaccine against the virus, and wherein an anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant protein vaccine or a purified protein vaccine against the virus, respectively; and/or wherein the effective amount is a dose equivalent to an at least 2-fold reduction in the standard of care dose of a live attenuated vaccine or an inactivated vaccine against the virus, and wherein an anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a live attenuated vaccine or an inactivated vaccine against the virus, respectively; and/or wherein the effective amount is a dose equivalent to an at least 2-fold reduction in the standard of care dose of a VLP vaccine against the virus, and wherein an anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a VLP vaccine against the virus.

78. The method of any one of paragraphs 72-77, wherein the effective amount is a total dose of 50 μg-1000 μg, optionally wherein the effective amount is a dose of 25 μg, 100 μg, 400 μg, or 500 μg administered to the subject a total of two times.

79. The method of any one of paragraphs 72-78, wherein the efficacy of the vaccine against the virus is greater than 65%; and/or wherein the vaccine immunizes the subject against the virus for up to 2 years or wherein the vaccine immunizes the subject against the virus for more than 2 years.

80. The method of any one of paragraphs 72-79, wherein the subject has an age of about 5 years old or younger or wherein the subject has an age of about 60 years old or older; and/or wherein the subject has a chronic pulmonary disease; and/or the subject has been exposed to the virus, wherein the subject is infected with the virus, or wherein the subject is at risk of infection by the virus; and/or wherein the subject is immunocompromised.

81. The respiratory virus vaccine of any one of paragraphs 1-71, comprising at least one (e.g., at least two, at least three, at least four, or at least five) RNA polynucleotide having an open reading frame encoding at least one (e.g., at least two, at least three, at least four, or at least five) antigenic polypeptide selected from hMPV antigenic polypeptides (SEQ ID NO: 5-8), PIV3 antigenic polypeptides (SEQ ID NO: 12-13), RSV antigenic polypeptides, MeV antigenic polypeptides (SEQ ID NO: 47-50) and BetaCoV antigenic polypeptides (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1; (SEQ ID NO: 24-34)), formulated in a cationic lipid nanoparticle

(a) having a molar ratio of about 20-60% cationic lipid, about 5-25% non-cationic lipid, about 25-55% sterol, and about 0.5-15% PEG-modified lipid, and/or

(b) comprising a compound of Formula (I) and/or Formula (II),

wherein the at least one (e.g., at least two, at least three, at least four, or at least five) RNA polynucleotide comprises at least one chemical modification.

82. The respiratory virus vaccine of any one of paragraphs 1-71, comprising at least one (e.g., at least two, at least three, at least four, or at least five) RNA polynucleotide having an open reading frame encoding at least one (e.g., at least two, at least three, at least four, or at least five) antigenic polypeptide selected from hMPV antigenic polypeptides (SEQ ID NO: 5-8), PIV3 antigenic polypeptides (SEQ ID NO: 12-13), RSV antigenic polypeptides, MeV antigenic polypeptides (SEQ ID NO: 47-50) and BetaCoV antigenic polypeptides (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1; (SEQ ID NO: 24-34)), formulated in a cationic lipid nanoparticle

(a) having a molar ratio of about 20-60% cationic lipid, about 5-25% non-cationic lipid, about 25-55% sterol, and about 0.5-15% PEG-modified lipid, and/or

(b) comprising at least one (e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14) Compound selected from Compounds 3, 18, 20, 25, 26, 29, 30, 60, 108-112 and 122.

83. The respiratory virus vaccine of paragraphs 81 or 82, wherein the at least one antigenic polypeptide is selected from hMPV antigentic polypeptides (e.g., SEQ ID NO: 5-8).

84. The respiratory virus vaccine of any one of paragraphs 81-83, wherein the at least one antigenic polypeptide is selected from PIV3 antigentic polypeptides (e.g., SEQ ID NO: 12-13).

85. The respiratory virus vaccine of any one of paragraphs 81-84, wherein the at least one antigenic polypeptide is selected from RSV antigentic polypeptides.

86. The respiratory virus vaccine of any one of paragraphs 81-85, wherein the at least one antigenic polypeptide is selected from MeV antigentic polypeptides (e.g., SEQ ID NO: 47-50).

87. The respiratory virus vaccine of any one of paragraphs 81-86, wherein the at least one antigenic polypeptide is selected from BetaCoV antigentic polypeptides (e.g., SEQ ID NO: 24-34).

88. The respiratory virus vaccine of paragraph 87, wherein the BetaCoV antigentic polypeptides are MERS antigentic polypeptides.

89. The respiratory virus vaccine of paragraph 87, wherein the BetaCoV antigentic polypeptides are SARS antigentic polypeptides.

90. The respiratory virus vaccine of any one of paragraphs 81-89, wherein the at least one (e.g., at least two, at least three, at least four, or at least five) RNA polynucleotide comprises at least one chemical modification (e.g., selected from pseudouridine, N1-methylpseudouridine, N1-ethylpseudouridine, 2-thiouridine, 4'-thiouridine, 5-methylcytosine, 5-methyluridine, 2-thio-1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-pseudouridine, 2-thio-5-aza-uridine, 2-thio-dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-pseudouridine, 4-methoxy-2-thio-pseudouridine, 4-methoxy-pseudouridine, 4-thio-1-methyl-pseudouridine, 4-thio-pseudouridine, 5-aza-uridine, dihydropseudouridine, 5-methoxyuridine and 2'-O-methyl uridine).

91. A respiratory virus vaccine, comprising:

at least one messenger ribonucleic acid (mRNA) polynucleotide having a 5' terminal cap, an open reading frame encoding at least one respiratory virus antigenic polypeptide, and a 3' polyA tail.

92. The vaccine of paragraph 91, wherein the at least one mRNA polynucleotide comprises a sequence identified by any one of SEQ ID NO: 57-80.

93. The vaccine of paragraph 91 or 92, wherein the 5' terminal cap is or comprises 7mG(5')ppp(5')NlmpNp.

94. The vaccine of any one of paragraphs 91-93, wherein 100% of the uracil in the open reading frame is modified to include N1-methyl pseudouridine at the 5-position of the uracil.

95. The vaccine of any one of paragraphs 91-94, wherein the vaccine is formulated in a lipid nanoparticle comprising: DLin-MC3-DMA; cholesterol; 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC); and polyethylene glycol (PEG) 2000-DMG.

96. The vaccine of paragraph 95, wherein the lipid nanoparticle further comprises trisodium citrate buffer, sucrose and water.

97. A respiratory syncytial virus (RSV) vaccine, comprising:

at least one messenger ribonucleic acid (mRNA) polynucleotide having a 5' terminal cap 7mG(5')ppp(5')NlmpNp, a sequence identified by any one of SEQ ID NO: 57-80 and a 3' polyA tail, formulated in a lipid nanoparticle comprising DLin-MC3-DMA, cholesterol, 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), and polyethylene glycol (PEG) 2000-DMG, wherein the uracil nucleotides of the sequence identified by any one of SEQ ID NO: 57-80 are modified to include N1-methyl pseudouridine at the 5-position of the uracil nucleotide.

This disclosure is not limited in its application to the details of construction and the arrangement of components set forth in the following description or illustrated in the drawings. The disclosure is capable of other embodiments and of being practiced or of being carried out in various ways. Also, the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of "including," "comprising," or "having," "containing," "involving," and variations thereof herein, is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

EXAMPLES

Example 1: Manufacture of Polynucleotides

According to the present disclosure, the manufacture of polynucleotides and/or parts or regions thereof may be accomplished utilizing the methods taught in International Publication WO2014/152027, entitled "Manufacturing Methods for Production of RNA Transcripts," the contents of which is incorporated herein by reference in its entirety.

Purification methods may include those taught in International Publication WO2014/152030 and International Publication WO2014/152031, each of which is incorporated herein by reference in its entirety.

Detection and characterization methods of the polynucleotides may be performed as taught in International Publication WO2014/144039, which is incorporated herein by reference in its entirety.

Characterization of the polynucleotides of the disclosure may be accomplished using polynucleotide mapping, reverse transcriptase sequencing, charge distribution analysis, detection of RNA impurities, or any combination of two or more of the foregoing. "Characterizing" comprises determining the RNA transcript sequence, determining the purity of the RNA transcript, or determining the charge heterogeneity of the RNA transcript, for example. Such methods are taught in, for example, International Publication WO2014/144711 and International Publication WO2014/144767, the content of each of which is incorporated herein by reference in its entirety.

Example 2: Chimeric Polynucleotide Synthesis

According to the present disclosure, two regions or parts of a chimeric polynucleotide may be joined or ligated using triphosphate chemistry. A first region or part of 100 nucleotides or less is chemically synthesized with a 5' monophosphate and terminal 3'desOH or blocked OH, for example. If the region is longer than 80 nucleotides, it may be synthesized as two strands for ligation.

If the first region or part is synthesized as a non-positionally modified region or part using in vitro transcription (IVT), conversion the 5'monophosphate with subsequent capping of the 3' terminus may follow.

Monophosphate protecting groups may be selected from any of those known in the art.

The second region or part of the chimeric polynucleotide may be synthesized using either chemical synthesis or IVT methods. IVT methods may include an RNA polymerase that can utilize a primer with a modified cap. Alternatively, a cap of up to 130 nucleotides may be chemically synthesized and coupled to the IVT region or part.

For ligation methods, ligation with DNA T4 ligase, followed by treatment with DNase should readily avoid concatenation.

The entire chimeric polynucleotide need not be manufactured with a phosphate-sugar backbone. If one of the regions or parts encodes a polypeptide, then such region or part may comprise a phosphate-sugar backbone.

Ligation is then performed using any known click chemistry, orthoclick chemistry, solulink, or other bioconjugate chemistries known to those in the art.

Synthetic Route

The chimeric polynucleotide may be made using a series of starting segments. Such segments include:

(a) a capped and protected 5' segment comprising a normal 3'OH (SEG. 1)

(b) a 5' triphosphate segment, which may include the coding region of a polypeptide and a normal 3'OH (SEG. 2)

(c) a 5' monophosphate segment for the 3' end of the chimeric polynucleotide (e.g., the tail) comprising cordycepin or no 3'OH (SEG. 3)

After synthesis (chemical or IVT), segment 3 (SEG. 3) may be treated with cordycepin and then with pyrophosphatase to create the 5' monophosphate.

Segment 2 (SEG. 2) may then be ligated to SEG. 3 using RNA ligase. The ligated polynucleotide is then purified and treated with pyrophosphatase to cleave the diphosphate. The treated SEG. 2-SEG. 3 construct may then be purified and SEG. 1 is ligated to the 5' terminus. A further purification step of the chimeric polynucleotide may be performed.

Where the chimeric polynucleotide encodes a polypeptide, the ligated or joined segments may be represented as: 5'UTR (SEG. 1), open reading frame or ORF (SEG. 2) and 3'UTR+PolyA (SEG. 3).

The yields of each step may be as much as 90-95%.

Example 3: PCR for cDNA Production

PCR procedures for the preparation of cDNA may be performed using 2×KAPA HIFI™ HotStart ReadyMix by Kapa Biosystems (Woburn, Mass.). This system includes 2×KAPA ReadyMix 12.5 μl; Forward Primer (10 μM) 0.75 μl; Reverse Primer (10 μM) 0.75 μl; Template cDNA 100 ng; and dH_2O diluted to 25.0 μl. The reaction conditions may be at 95° C. for 5 min. The reaction may be performed for 25 cycles of 98° C. for 20 sec, then 58° C. for 15 sec, then 72° C. for 45 sec, then 72° C. for 5 min, then 4° C. to termination.

The reaction may be cleaned up using Invitrogen's PURELINK™ PCR Micro Kit (Carlsbad, Calif.) per manufacturer's instructions (up to 5 μg). Larger reactions may require a cleanup using a product with a larger capacity. Following the cleanup, the cDNA may be quantified using the NANODROP™ and analyzed by agarose gel electrophoresis to confirm that the cDNA is the expected size. The cDNA may then be submitted for sequencing analysis before proceeding to the in vitro transcription reaction.

Example 4: In Vitro Transcription (IVT)

The in vitro transcription reaction generates RNA polynucleotides. Such polynucleotides may comprise a region or part of the polynucleotides of the disclosure, including chemically modified RNA (e.g., mRNA) polynucleotides. The chemically modified RNA polynucleotides can be uniformly modified polynucleotides. The in vitro transcription reaction utilizes a custom mix of nucleotide triphosphates (NTPs). The NTPs may comprise chemically modified NTPs, or a mix of natural and chemically modified NTPs, or natural NTPs.

A typical in vitro transcription reaction includes the following:

1)	Template cDNA	1.0 μg
2)	10x transcription buffer (400 mM Tris-HCl pH 8.0, 190 mM $MgCl_2$, 50 mM DTT, 10 mM Spermidine)	2.0 μl
3)	Custom NTPs (25 mM each)	0.2 μl
4)	RNase Inhibitor	20 U
5)	T7 RNA polymerase	3000 U
6)	dH_20	up to 20.0 μl. and
7)	Incubation at 37° C. for 3 hr-5 hrs.	

The crude IVT mix may be stored at 4° C. overnight for cleanup the next day. 1 U of RNase-free DNase may then be used to digest the original template. After 15 minutes of incubation at 37° C., the mRNA may be purified using Ambion's MEGACLEAR™ Kit (Austin, Tex.) following the manufacturer's instructions. This kit can purify up to 500 μg of RNA. Following the cleanup, the RNA polynucleotide may be quantified using the NanoDrop and analyzed by agarose gel electrophoresis to confirm the RNA polynucleotide is the proper size and that no degradation of the RNA has occurred.

Example 5: Enzymatic Capping

Capping of a RNA polynucleotide is performed as follows where the mixture includes: IVT RNA 60 μg-180 μg and dH_2O up to 72 μl. The mixture is incubated at 65° C. for 5 minutes to denature RNA, and then is transferred immediately to ice.

The protocol then involves the mixing of 10× Capping Buffer (0.5 M Tris-HCl (pH 8.0), 60 mM KCl, 12.5 mM $MgCl_2$) (10.0 μl); 20 mM GTP (5.0 μl); 20 mM S-Adenosyl Methionine (2.5 μl); RNase Inhibitor (100 U); 2'-O-Methyltransferase (400U); Vaccinia capping enzyme (Guanylyl transferase) (40 U); dH_2O (Up to 28 μl); and incubation at 37° C. for 30 minutes for 60 μg RNA or up to 2 hours for 180 μg of RNA.

The RNA polynucleotide may then be purified using Ambion's MEGACLEAR™ Kit (Austin, Tex.) following the manufacturer's instructions. Following the cleanup, the RNA may be quantified using the NANODROP™ (ThermoFisher, Waltham, Mass.) and analyzed by agarose gel electrophoresis to confirm the RNA polynucleotide is the proper size and that no degradation of the RNA has occurred. The RNA polynucleotide product may also be sequenced by running a reverse-transcription-PCR to generate the cDNA for sequencing.

Example 6: PolyA Tailing Reaction

Without a poly-T in the cDNA, a poly-A tailing reaction must be performed before cleaning the final product. This is done by mixing capped IVT RNA (100 μl); RNase Inhibitor (20 U); 10× Tailing Buffer (0.5 M Tris-HCl (pH 8.0), 2.5 M NaCl, 100 mM $MgCl_2$) (12.0 μl); 20 mM ATP (6.0 μl); Poly-A Polymerase (20 U); dH_2O up to 123.5 μl and incubation at 37° C. for 30 min. If the poly-A tail is already in the transcript, then the tailing reaction may be skipped and proceed directly to cleanup with Ambion's MEGACLEAR™ kit (Austin, Tex.) (up to 500 μg). Poly-A Polymerase may be a recombinant enzyme expressed in yeast.

It should be understood that the processivity or integrity of the polyA tailing reaction may not always result in an exact size polyA tail. Hence, polyA tails of approximately between 40-200 nucleotides, e.g., about 40, 50, 60, 70, 80, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 150-165, 155, 156, 157,

158, 159, 160, 161, 162, 163, 164 or 165 are within the scope of the present disclosure.

Example 7. Natural 5' Caps and 5' Cap Analogues

5'-capping of polynucleotides may be completed concomitantly during the in vitro-transcription reaction using the following chemical RNA cap analogs to generate the 5'-guanosine cap structure according to manufacturer protocols: 3'-O-Me-m7G(5')ppp(5') G [the ARCA cap]; G(5')ppp(5')A; G(5')ppp(5')G; m7G(5')ppp(5')A; m7G(5')ppp(5')G (New England BioLabs, Ipswich, Mass.). 5'-capping of modified RNA may be completed post-transcriptionally using a Vaccinia Virus Capping Enzyme to generate the "Cap 0" structure: m7G(5')ppp(5')G (New England BioLabs, Ipswich, Mass.). Cap 1 structure may be generated using both Vaccinia Virus Capping Enzyme and a 2'-O methyl-transferase to generate: m7G(5')ppp(5')G-2'-O-methyl. Cap 2 structure may be generated from the Cap 1 structure followed by the 2'-O-methylation of the 5'-antepenultimate nucleotide using a 2'-O methyl-transferase. Cap 3 structure may be generated from the Cap 2 structure followed by the 2'-O-methylation of the 5'-preantepenultimate nucleotide using a 2'-O methyl-transferase. Enzymes are preferably derived from a recombinant source.

When transfected into mammalian cells, the modified mRNAs have a stability of between 12-18 hours or more than 18 hours, e.g., 24, 36, 48, 60, 72 or greater than 72 hours.

Example 8: Capping Assays

Protein Expression Assay

Polynucleotides (e.g., mRNA) encoding a polypeptide, containing any of the caps taught herein, can be transfected into cells at equal concentrations. The amount of protein secreted into the culture medium can be assayed by ELISA at 6, 12, 24 and/or 36 hours post-transfection. Synthetic polynucleotides that secrete higher levels of protein into the medium correspond to a synthetic polynucleotide with a higher translationally-competent cap structure.

Purity Analysis Synthesis

RNA (e.g., mRNA) polynucleotides encoding a polypeptide, containing any of the caps taught herein can be compared for purity using denaturing Agarose-Urea gel electrophoresis or HPLC analysis. RNA polynucleotides with a single, consolidated band by electrophoresis correspond to the higher purity product compared to polynucleotides with multiple bands or streaking bands. Chemically modified RNA polynucleotides with a single HPLC peak also correspond to a higher purity product. The capping reaction with a higher efficiency provides a more pure polynucleotide population.

Cytokine Analysis

RNA (e.g., mRNA) polynucleotides encoding a polypeptide, containing any of the caps taught herein can be transfected into cells at multiple concentrations. The amount of pro-inflammatory cytokines, such as TNF-alpha and IFN-beta, secreted into the culture medium can be assayed by ELISA at 6, 12, 24 and/or 36 hours post-transfection. RNA polynucleotides resulting in the secretion of higher levels of pro-inflammatory cytokines into the medium correspond to a polynucleotides containing an immune-activating cap structure.

Capping Reaction Efficiency

RNA (e.g., mRNA) polynucleotides encoding a polypeptide, containing any of the caps taught herein can be analyzed for capping reaction efficiency by LC-MS after nuclease treatment. Nuclease treatment of capped polynucleotides yield a mixture of free nucleotides and the capped 5'-5-triphosphate cap structure detectable by LC-MS. The amount of capped product on the LC-MS spectra can be expressed as a percent of total polynucleotide from the reaction and correspond to capping reaction efficiency. The cap structure with a higher capping reaction efficiency has a higher amount of capped product by LC-MS.

Example 9: Agarose Gel Electrophoresis of Modified RNA or RT PCR Products

Individual RNA polynucleotides (200-400 ng in a 20 μl volume) or reverse transcribed PCR products (200-400 ng) may be loaded into a well on a non-denaturing 1.2% Agarose E-Gel (Invitrogen, Carlsbad, Calif.) and run for 12-15 minutes, according to the manufacturer protocol.

Example 10: Nanodrop Modified RNA Quantification and UV Spectral Data

Chemically modified RNA polynucleotides in TE buffer (1 μl) are used for Nanodrop UV absorbance readings to quantitate the yield of each polynucleotide from an chemical synthesis or in vitro transcription reaction.

Example 11: Formulation of Modified mRNA Using Lipidoids

RNA (e.g., mRNA) polynucleotides may be formulated for in vitro experiments by mixing the polynucleotides with the lipidoid at a set ratio prior to addition to cells. In vivo formulation may require the addition of extra ingredients to facilitate circulation throughout the body. To test the ability of these lipidoids to form particles suitable for in vivo work, a standard formulation process used for siRNA-lipidoid formulations may be used as a starting point. After formation of the particle, polynucleotide is added and allowed to integrate with the complex. The encapsulation efficiency is determined using a standard dye exclusion assays.

Example 12: Immunogenicity Study

The instant study is designed to test the immunogenicity in mice of candidate hMPV vaccines comprising a mRNA polynucleotide encoding Fusion (F) glycoprotein, major surface glycoprotein G, or a combination thereof, obtained from hMPV.

Mice are immunized intravenously (IV), intramuscularly (IM), or intradermally (ID) with candidate vaccines. Candidate vaccines are chemically modified or unmodified. A total of four immunizations are given at 3-week intervals (i.e., at weeks 0, 3, 6, and 9), and sera are collected after each immunization until weeks 33-51. Serum antibody titers against Fusion (F) glycoprotein or major surface glycoprotein (G) protein are determined by ELISA. Sera collected from each mouse during weeks 10-16 are pooled, and total IgG purified. Purified antibodies are used for immunoelectron microscopy, antibody-affinity testing, and in vitro protection assays.

Example 13: hMPV Rodent Challenge

The instant study is designed to test the efficacy in cotton rats of candidate hMPV vaccines against a lethal challenge using an hMPV vaccine comprising mRNA encoding Fusion

(F) glycoprotein, major surface glycoprotein G, or a combination of both antigens obtained from hMPV. Cotton rats are challenged with a lethal dose of the hMPV.

Animals are immunized intravenously (IV), intramuscularly (IM), or intradermally (ID) at week 0 and week 3 with candidate hMPV vaccines with and without adjuvant. Candidate vaccines are chemically modified or unmodified. The animals are then challenged with a lethal dose of hMPV on week 7 via IV, IM or ID. Endpoint is day 13 post infection, death or euthanasia. Animals displaying severe illness as determined by >30% weight loss, extreme lethargy or paralysis are euthanized. Body temperature and weight are assessed and recorded daily.

In experiments where a lipid nanoparticle (LNP) formulation is used, the formulation may include a cationic lipid, non-cationic lipid, PEG lipid and structural lipid in the ratios 50:10:1.5:38.5. The cationic lipid is DLin-KC2-DMA (50 mol %) or DLin-MC3-DMA (50 mol %), the non-cationic lipid is DSPC (10 mol %), the PEG lipid is PEG-DOMG (1.5 mol %) and the structural lipid is cholesterol (38.5 mol %), for example.

Example 14: Immunogenicity of hMPV mRNA Vaccine in BALB/c Mice

The instant study was designed to test the immunogenicity in BALB/c mice of hMPV vaccines comprising an mRNA polynucleotide encoding the hMPV Fusion (F) glycoprotein. The mRNA polynucleotide encodes the full-length fusion protein and comprises the wild-type nucleotide sequence obtained from the hMPV A2a strain. Mice were divided into 3 groups (n=8 for each group) and immunized intramuscularly (IM) with PBS, a 10 μg dose of mRNA vaccines encoding hMPV fusion protein, or a 2 μg dose of mRNA vaccines encoding hMPV fusion protein. A total of two immunizations were given at 3-week intervals (i.e., at weeks 0, and 3 weeks), and sera were collected after each immunization according to the schedule described in Table 1. Serum antibody titers against hMPV fusion glycoprotein were determined by ELISA and antibodies were detected in the sera collected on day 14 onward. Both vaccine doses tested induced comparable levels of immune response in mice (FIGS. **2**A-**2**C).

Additionally, mice sera were used for IgG isotyping (FIGS. **3**A-**3**C). Both hMPV fusion protein-specific IgG1 and IgG2a were detected in mice sera. hMPV fusion protein mRNA vaccine also induced Th1 and Th2 cytokine responses, with a Th1 bias.

Sera from mice immunized with either 10 μg or 2 μg doses of the hMPV fusion protein mRNA vaccine contain neutralizing antibodies. The ability of these antibodies to neutralize hMPV B2 strain was also tested. The antibody-containing sera successfully neutralized the hMPV B2 virus (FIG. **4**).

Example 15: T-Cell Stimulation

The instant study was designed to test T-cell stimulation in the splenocytes of mice immunized with mRNA vaccines encoding hMPV fusion protein, as described herein. Immunization of BALB/c mice was performed as described in Example 14. The splenocytes for each group were pooled and split into two parts. One part of splenocytes from each group of mice was stimulated with hMPV-free media, Concanavalin A or a hMPV fusion protein peptide pool comprising 15-mers (15 amino acids long); while the other part of splenocytes from each group of mice was stimulated with hMPV-free media, Concanavalin A or inactivated hMPV virus. Secreted mouse cytokines were measured using the Meso Scale Discovery (MSD) assay.

Cytokines specific to Th1 or Th2 responses were measured. For Th1 response, IFN-γ, IL2 and IL12 were detected from splenocytes stimulated with the hMPV fusion protein peptide pool at a level comparable to that of Concanavalin A (FIGS. **5**A-**5**C). For a Th2 response, the hMPV fusion protein peptide pool induced the secretion of detectable IL10, TNF-α, IL4 and IL, but not IL5, while Concanavalin A stimulated the secretion of all the above-mentioned Th2 cytokines (FIGS. **6**A-**6**E) at a much higher level.

In contrast, inactivated hMPV virus only induced the secretion of IL2 in the Th1 response comparable to that of Concanavalin A (FIGS. **7**A-**7**C). For the Th2 response, the inactivated hMPV virus induced the secretion of detectable IL10, TNF-α, IL4 and IL6, but not IL5, while Concanavalin A stimulated the secretion of all the above-mentioned Th2 cytokines (FIGS. **8**A-**8**E) at a much higher level.

Example 16: hMPV Rodent Challenge in Cotton Rats Immunized with mRNA Vaccine Encoding hMPV Fusion Protein

The instant study was designed to test the efficacy in cotton rats of hMPV vaccines against a lethal challenge. mRNA vaccines encoding hMPV fusion protein were used. The mRNA polynucleotide encodes a full-length fusion protein and comprises the wild-type nucleotide sequence obtained from the hMPV A2a strain.

Cotton rats were immunized intramuscularly (IM) at week 0 and week 3 with the mRNA vaccines encoding hMPV fusion protein with either 2 μg or 10 μg doses for each immunization. The animals were then challenged with a lethal dose of hMPV in week 7 post initial immunization via IV, IM or ID. The endpoint was day 13 post infection, death or euthanasia. Viral titers in the noses and lungs of the cotton rats were measured. The results (FIGS. **9**A and **9**B) show that a 10 μg dose of mRNA vaccine protected the cotton mice 100% in the lung and drastically reduced the viral titer in the nose after challenge (~2 log reduction). Moreover, a 2 μg dose of mRNA vaccine showed a 1 log reduction in lung viral titer in the cotton mice challenged.

Further, the histopathology of the lungs of the cotton mice immunized and challenged showed no pathology associated with vaccine-enhanced disease (FIG. **10**).

Example 17. Immunogenicity Study

The instant study is designed to test the immunogenicity in mice of candidate PIV3 vaccines comprising a mRNA polynucleotide encoding hemagglutinin-neuraminidase or fusion protein (F or F0) obtained from PIV3.

Mice are immunized intravenously (IV), intramuscularly (IM), or intradermally (ID) with candidate vaccines. Candidate vaccines are chemically modified or unmodified. A total of four immunizations are given at 3-week intervals (i.e., at weeks 0, 3, 6, and 9), and sera are collected after each immunization until weeks 33-51. Serum antibody titers against hemagglutinin-neuraminidase or fusion protein (F or F0) are determined by ELISA. Sera collected from each mouse during weeks 10-16 are, optionally, pooled, and total IgGs are purified. Purified antibodies are used for immuno-electron microscopy, antibody-affinity testing, and in vitro protection assays.

Example 18: PIV3 Rodent Challenge

The instant study is designed to test the efficacy in cotton rats of candidate PIV3 vaccines against a lethal challenge

using a PIV3 vaccine comprising mRNA encoding hemagglutinin-neuraminidase or fusion protein (F or F0) obtained from PIV3. Cotton rats are challenged with a lethal dose of the PIV3.

Animals are immunized intravenously (IV), intramuscularly (IM), or intradermally (ID) at week 0 and week 3 with candidate PIV3 vaccines with and without adjuvant. Candidate vaccines are chemically modified or unmodified. The animals are then challenged with a lethal dose of PIV3 on week 7 via IV, IM or ID. Endpoint is day 13 post infection, death or euthanasia. Animals displaying severe illness as determined by >30% weight loss, extreme lethargy or paralysis are euthanized. Body temperature and weight are assessed and recorded daily.

In experiments where a lipid nanoparticle (LNP) formulation is used, the formulation may include a cationic lipid, non-cationic lipid, PEG lipid and structural lipid in the ratios 50:10:1.5:38.5. The cationic lipid is DLin-KC2-DMA (50 mol %) or DLin-MC3-DMA (50 mol %), the non-cationic lipid is DSPC (10 mol %), the PEG lipid is PEG-DOMG (1.5 mol %) and the structural lipid is cholesterol (38.5 mol %), for example.

Example 19: hMPV/PIV Cotton Rat Challenge

The instant study was designed to test the efficacy in cotton rats of candidate hMPV mRNA vaccines, PIV3 mRNA vaccines, or hMPV/PIV combination mRNA vaccines against a lethal challenge using PIV3 strain or hMPV/A2 strain. The study design is shown in Table 9.

Cotton rats of 10-12 weeks old were divided into 12 groups (n=5), and each group was vaccinated with mRNA vaccines indicated in Table 9. The PIV3 vaccine comprises mRNA encoding hemagglutinin-neuraminidase or fusion protein (F or F0) obtained from PIV3. The hMPV mRNA vaccine encodes the full-length hMPV fusion protein. The hMPV/PIV combination mRNA vaccine is a mixture of the PIV3 vaccine and hMPV vaccine at a 1:1 ratio.

Cotton rats were immunized intramuscularly (IM) at week 0 and week 3 with candidate vaccines with the doses indicated in Table 9. Cotton rats immunized with hMPV mRNA vaccines or hMPV/PIV combination mRNA vaccines were challenged with a lethal dose of hMPV/A2 strain on week 7 via IM. Cotton rats immunized with PIV mRNA vaccines or hMPV/PIV combination mRNA vaccines were challenged with a lethal dose of PIV3 strain on week 7 via IM.

The endpoint was day 13 post infection, death or euthanasia. Animals displaying severe illness as determined by >30% weight loss, extreme lethargy or paralysis were euthanized. Body temperature and weight were assessed and recorded daily.

Lung and nose hMPV/A2 (FIG. **12**) or PIV3 (FIG. **13**) viral titers were assessed. Lung histopathology of the immunized and challenged cotton rat immunized and challenged were assessed to determine pathology associated with vaccine enhance disease. Neutralization antibody titers in the serum of immunized cotton rats on day 0 and 42 post immunization were assessed (FIG. **11**).

hMPV/A2 (FIG. **14**) or PIV3 (FIG. **15**) neutralizing antibody titers in the serum samples of the immunized cotton rat 42 days post immunization were measured. All mRNA vaccines tested induced strong neutralizing antibodies cotton rats. Lung histopathology of the immunized cotton rats were also evaluated (FIG. **16**). Low occurrence of alevolitis and interstitial pneumonia was observed, indicating no antibody-dependent enhancement (ADE) of hMPV or PIV associated diseases.

Example 20: *Betacoronavirus* Immunogenicity Study

The instant study is designed to test the immunogenicity in rabbits of candidate *Betacoronavirus* (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1 or a combination thereof) vaccines comprising a mRNA polynucleotide encoding the spike (S) protein, the S1 subunit (S1) of the spike protein, or the S2 subunit (S2) of the spike protein obtained from a *Betacoronavirus* (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1).

Rabbits are vaccinated on week 0 and 3 via intravenous (IV), intramuscular (IM), or intradermal (ID) routes. One group remains unvaccinated and one is administered inactivated *Betacoronavirus*. Serum is collected from each rabbit on weeks 1, 3 (pre-dose) and 5. Individual bleeds are tested for anti-S, anti-S1 or anti-S2 activity via a virus neutralization assay from all three time points, and pooled samples from week 5 only are tested by Western blot using inactivated *Betacoronavirus* (e.g., inactivated MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1).

In experiments where a lipid nanoparticle (LNP) formulation is used, the formulation may include a cationic lipid, non-cationic lipid, PEG lipid and structural lipid in the ratios 50:10:1.5:38.5. The cationic lipid is DLin-KC2-DMA (50 mol %) or DLin-MC3-DMA (50 mol %), the non-cationic lipid is DSPC (10 mol %), the PEG lipid is PEG-DOMG (1.5 mol %) and the structural lipid is cholesterol (38.5 mol %), for example.

Example 21: *Betacoronavirus* Challenge

The instant study is designed to test the efficacy in rabbits of candidate *Betacoronavirus* (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-HKU1 or a combination thereof) vaccines against a lethal challenge using a *Betacoronavirus* (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-HKU1 or a combination thereof) vaccine comprising mRNA encoding the spike (S) protein, the S1 subunit (S1) of the spike protein, or the S2 subunit (S2) of the spike protein obtained from *Betacoronavirus* (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1). Rabbits are challenged with a lethal dose (10×LD90; ~100 plaque-forming units; PFU) of *Betacoronavirus* (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1).

The animals used are 6-8 week old female rabbits in groups of 10. Rabbits are vaccinated on weeks 0 and 3 via an IM, ID or IV route of administration. Candidate vaccines are chemically modified or unmodified. Rabbit serum is tested for microneutralization (see Example 14). Rabbits are then challenged with ~1 LD90 of *Betacoronavirus* (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1) on week 7 via an IN, IM, ID or IV route of administration. Endpoint is day 13 post infection, death or euthanasia. Animals displaying severe illness as determined by >30%

weight loss, extreme lethargy or paralysis are euthanized. Body temperature and weight are assessed and recorded daily.

Example 22: Microneutralization Assay

Nine serial 2-fold dilutions (1:50-1:12,800) of rabbit serum are made in 50 μl virus growth medium (VGM) with trypsin in 96 well microtiter plates. Fifty microliters of virus containing ~50 pfu of *Betacoronavirus* (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1) is added to the serum dilutions and allowed to incubate for 60 minutes at room temperature (RT). Positive control wells of virus without sera and negative control wells without virus or sera are included in triplicate on each plate. While the serum-virus mixtures incubate, a single cell suspension of Madin-Darby Canine-Kidney cells are prepared by trypsinizing (Gibco 0.5% bovine pancrease trypsin in EDTA) a confluent monolayer and suspended cells are transferred to a 50 ml centrifuge tube, topped with sterile PBS and gently mixed. The cells are then pelleted at 200 g for 5 minutes, supernatant aspirated and cells resuspended in PBS. This procedure is repeated once and the cells are resuspended at a concentration of 3×10^5/ml in VGM with porcine trypsin. Then, 100 μl of cells are added to the serum-virus mixtures and the plates incubated at 35° C. in CO_2 for 5 days. The plates are fixed with 80% acetone in phosphate buffered saline (PBS) for 15 minutes at RT, air dried and then blocked for 30 minutes containing PBS with 0.5% gelatin and 2% FCS. An antibody to the S proteins, 51 protein or S2 protein is diluted in PBS with 0.5% gelatin/2% FCS/0.5% Tween 20 and incubated at RT for 2 hours. Wells are washed and horseradish peroxidase-conjugated goat anti-mouse IgG added, followed by another 2 hour incubation. After washing, 0-phenylenediamine dihydrochloride is added and the neutralization titer is defined as the titer of serum that reduced color development by 50% compared to the positive control wells.

Example 23: MERS CoV Vaccine Immunogenicity Study in Mice

The instant study was designed to test the immunogenicity in mice of candidate MERS-CoV vaccines comprising a mRNA polynucleotide encoding the full-length Spike (S) protein, or the S2 subunit (S2) of the Spike protein obtained from MERS-CoV.

Mice were vaccinated with a 10 μg dose of MERS-CoV mRNA vaccine encoding either the full-length MERS-CoV Spike (S) protein, or the S2 subunit (S2) of the Spike protein on days 0 and 21. Sera were collected from each mice on days 0, 21, 42, and 56. Individual bleeds were tested for anti-S, anti-S2 activity via a virus neutralization assay from all four time points.

As shown in FIG. **17**, the MERS-CoV vaccine encoding the full-length S protein induced strong immune response after the boost dose on day 21. Further, full-length S protein vaccine generated much higher neutralizing antibody titers as compared to S2 alone (FIG. **18**).

Example 24: MERS CoV Vaccine Immunogenicity Study in New Zealand White Rabbits

The instant study was designed to test the immunogenicity of candidate MERS-CoV mRNA vaccines encoding the full-length Spike (S) protein. The New Zealand white rabbits used in this study weighed about 4-5 kg. The rabbits were divided into three groups (Group 1a, Group 1b, and Group 2, n=8). Rabbits in Group 1a were immunized intramuscularly (IM) with one 20 μg dose of the MERS-CoV mRNA vaccine encoding the full-length Spike protein on day 0. Rabbits in Group 1b were immunized intramuscularly (IM) with one 20 μg dose of the MERS-CoV mRNA vaccine encoding the full-length Spike protein on day 0, and again on day 21 (booster dose). Group 2 received placebo (PBS). The immunized rabbits were then challenged and samples were collected 4 days after challenge. The viral loads in the lungs, bronchoalveolar lavage (Bal), nose, and throat of the rabbits were determined, e.g., via quantitative PCR. Replicating virus in the lung tissues of the rabbits were also detected. Lung histopathology were evaluated and the neutralizing antibody titers in serum samples of the rabbits were determined.

Two 20 μg doses of MERS-CoV mRNA vaccine resulted in a 3 log reduction of viral load in the nose and led to complete protection in the throat of the New Zealand white rabbits (FIG. **19**A). Two 20 μg doses of MERS-CoV mRNA vaccine also resulted in a 4 log reduction of viral load in the BAL of the New Zealand white rabbits (FIG. **19**B). One 20 μg dose of MERS-CoV mRNA vaccine resulted in a 2 log reduction of viral load, while two 20 μg doses of MERS-CoV mRNA vaccine resulted in an over 4 log reduction of viral load in the lungs of the New Zealand white rabbits (FIG. **19**C).

Quantitative PCR results show that two 20 μg doses of MERS-CoV mRNA vaccine reduced over 99% (2 log) of viruses in the lungs of New Zealand white rabbits (FIG. **20**A). No replicating virus were detected in the lungs (FIG. **20**B).

Further, as shown in FIG. **21**, two 20 μg doses of MERS-CoV mRNA vaccine induced significant amount of neutralizing antibodies against MERS-CoV (EC_{50} between 500-1000). The MERS-CoV mRNA vaccine induced antibody titer is 3-5 fold better than any other vaccines tested in the same model.

Example 25: Immunogenicity Study

The instant study is designed to test the immunogenicity in mice of candidate MeV vaccines comprising a mRNA polynucleotide encoding MeV hemagglutinin (HA) protein, MeV Fusion (F) protein or a combination of both.

Mice are immunized intravenously (IV), intramuscularly (IM), or intradermally (ID) with candidate vaccines. Up to three immunizations are given at 3-week intervals (i.e., at weeks 0, 3, 6, and 9), and sera are collected after each immunization until weeks 33-51. Serum antibody titers against MeV HA protein or MeV F protein are determined by ELISA.

Example 26: MeV Rodent Challenge

The instant study is designed to test the efficacy in transgenic mice of candidate MeV vaccines against a lethal challenge using a MeV vaccine comprising mRNA encoding MeV HA protein or MeV F protein. The transgenic mice express human receptor CD46 or signaling lymphocyte activation molecule (SLAM) (also referred to as CD150). Humans are the only natural host for MeV infection, thus transgenic lines are required for this study. CD46 is a complement regulatory protein that protects host tissue from complement deposition by binding to complement components C3b and C4b. Its expression on murine fibroblast and

lymphoid cell lines renders these otherwise refractory cells permissive for MeV infection, and the expression of CD46 on primate cells parallels the clinical tropism of MeV infection in humans and nonhuman primates (Rall G F et al. *PNAS USA* 1997; 94(9):4659-63). SLAM is a type 1 membrane glycoprotein belonging to the immunoglobulin superfamily. It is expressed on the surface of activated lymphocytes, macrophages, and dendritic cells and is thought to play an important role in lymphocyte signaling. SLAM is a receptor for both wild-type and vaccine MeV strains (Sellin C I et al. *J Virol.* 2006; 80(13):6420-29).

CD46 or SLAM/CD150 transgenic mice are challenged with a lethal dose of the MeV. Animals are immunized intravenously (IV), intramuscularly (IM), or intradermally (ID) at week 0 and week 3 with candidate MeV vaccines with and without adjuvant. The animals are then challenged with a lethal dose of MeV on week 7 via IV, IM or ID. Endpoint is day 13 post infection, death or euthanasia. Animals displaying severe illness as determined by >30% weight loss, extreme lethargy or paralysis are euthanized. Body temperature and weight are assessed and recorded daily.

In experiments where a lipid nanoparticle (LNP) formulation is used, the formulation may include a cationic lipid, non-cationic lipid, PEG lipid and structural lipid in the ratios 50:10:1.5:38.5. The cationic lipid is DLin-KC2-DMA (50 mol %), the non-cationic lipid is DSPC (10 mol %), the PEG lipid is PEG-DOMG (1.5 mol %) and the structural lipid is cholesterol (38.5 mol %), for example.

TABLE 1

hMPV Immunogenicity studies bleeding schedule

	Animal groups		Day							
	(n = 8)	vaccine	−2	0	7	14	21	28	35	56
Placebo	Group 1 (n = 8)	PBS (IM)	Pre-Bleed	Prime	Bleeds	Bleeds	Bleeds/ Boost	Bleeds	Bleeds	Harvest Spleens/ Terminal Bleeds
10 μg Dose	Group 2 (n = 8)	10 μg (IM)								
2 μg Dose	Group 3 (n = 8)	2 μg (IM)								

Total n = 24

Each of the sequences described herein encompasses a chemically modified sequence or an unmodified sequence which includes no nucleotide modifications.

TABLE 2

Description	Sequence	SEQ ID NO:
	hMPV Nucleic Acid Sequences	
gi|122891979|gb| EF051124.1| Human metapneumo virus isolate TN/92-4 fusion protein gene, complete genome	ATGAGCTGGAAGGTGGTGATTATCTTCAGCCTGCTGATTA CACCTCAACACGGCCTGAAGGAGAGCTACCTGGAAGAGA GCTGCTCCACCATCACCGAGGGCTACCTGAGCGTGCTGC GGACCGGCTGGTACACCAACGTGTTCACCCTGGAGGTGG GCGACGTGGAGAACCTGACCTGCAGCGACGGCCCTAGCC TGATCAAGACCGAGCTGGACCTGACCAAGAGCGCTCTGA GAGAGCTGAAGACCGTGTCCGCCGACCAGCTGGCCAGAG AGGAACAGATCGAGAACCCTCGGCAGAGCAGATTCGTGC TGGGCGCCATCGCTCTGGGAGTCGCCGCTGCCGCTGCAG TGACAGCTGGAGTGGCCATTGCTAAGACCATCAGACTGG AAAGCGAGGTGACAGCCATCAACAATGCCCTGAAGAAG ACCAACGAGGCCGTGAGCACCCTGGGCAATGGAGTGAGA GTGCTGGCCACAGCCGTGCGGGAGCTGAAGGACTTCGTG AGCAAGAACCTGACCAGAGCCATCAACAAGAACAAGTG CGACATCGATGACCTGAAGATGGCCGTGAGCTTCTCCCA GTTCAACAGACGGTTCCTGAACGTGGTGAGACAGTTCTC CGACAACGCTGGAATCACACCTGCCATTAGCCTGGACCT GATGACCGACGCCGAGCTGGCTAGAGCCGTGCCCAACAT GCCCACCAGCGCTGGCCAGATCAAGCTGATGCTGGAGAA CAGAGCCATGGTGCGGAGAAAGGGCTTCGGCATCCTGAT TGGGGTGTATGGAAGCTCCGTGATCTACATGGTGCAGCT GCCCATCTTCGGCGTGATCGACACACCCTGCTGGATCGTG AAGGCCGCTCCTAGCTGCTCCGAGAAGAAAGGAAACTAT GCCTGTCTGCTGAGAGAGGACCAGGGCTGGTACTGCCAG AACGCCGGAAGCACAGTGTACTATCCCAACGAGAAGGAC TGCGAGACCAGAGGCGACCACGTGTTCTGCGACACCGCT GCCGGAATCAACGTGGCCGAGCAGAGCAAGGAGTGCAA CATCAACATCAGCACAACCAACTACCCCTGCAAGGTGAG CACCGGACGGCACCCCATCAGCATGGTGGCTCTGAGCCC TCTGGGCGCTCTGGTGGCCTGCTATAAGGGCGTGTCCTGT AGCATCGGCAGCAATCGGGTGGGCATCATCAAGCAGCTG	1

TABLE 2 -continued

Description	Sequence	SEQ ID NO:
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	ACCGTGACCATCGACAACACCGTGTACCAGCTGAGCAAG	
	GTGGAGGGCGAGCAGCACGTGATCAAGGGCAGACCCGT	
	GAGCTCCAGCTTCGACCCCATCAAGTTCCCTGAGGACCA	
	GTTCAACGTGGCCCTGGACCAGGTGTTTGAGAACATCGA	
	GAACAGCCAGGCCCTGGTGGACCAGAGCAACAGAATCCT	
	GTCCAGCGCTGAGAAGGGCAACACCGGCTTCATCATTGT	
	GATCATTCTGATCGCCGTGCTGGGCAGCTCCATGATCCTG	
	GTGAGCATCTTCATCATTATCAAGAAGACCAAGAAACCC	
	ACCGGAGCCCCTCCTGAGCTGAGCGGCGTGACCAACAAT	
	GGCTTCATTCCCCACAACTGA	
gb|AY525843.1|: 3065-4684 Human metapneumo virus isolate NL/1/99, complete genome	ATGTCTTGGAAAGTGATGATCATCATTTCGTTACTCATAA	2
	CACCCCAGCACGGGCTAAAGGAGAGTTATTTGGAAGAAT	
	CATGTAGTACTATAACTGAGGGATACCTCAGTGTTTTAAG	
	AACAGGCTGGTACACTAATGTCTTCACATTAGAAGTTGGT	
	GATGTTGAAAATCTTACATGTACTGATGGACCTAGCTTAA	
	TCAAAACAGAACTTGATCTAACAAAAAGTGCTTTAAGGG	
	AACTCAAAACAGTCTCTGCTGATCAGTTGGCGAGAGAGG	
	AGCAAATTGAAAATCCCAGACAATCAAGATTTGTCTTAG	
	GTGCGATAGCTCTCGGAGTTGCTACAGCAGCAGCAGTCA	
	CAGCAGGCATTGCAATAGCCAAAACCATAAGGCTTGAGA	
	GTGAGGTGAATGCAATTAAAGGTGCTCTCAAACAAACTA	
	ATGAAGCAGTATCCACATTAGGGAATGGTGTGCGGGTCC	
	TAGCCACTGCAGTGAGAGAGCTAAAAGAATTTGTGAGCA	
	AAAACCTGACTAGTGCAATCAACAGGAACAAATGTGACA	
	TTGCTGATCTGAAGATGGCTGTCAGCTTCAGTCAATTCAA	
	CAGAAGATTTCTAAATGTTGTGCGGCAGTTTTCAGACAAT	
	GCAGGGATAACACCAGCAATATCATTGGACCTGATGACT	
	GATGCTGAGTTGGCCAGAGCTGTATCATACATGCCAACA	
	TCTGCAGGGCAGATAAAACTGATGTTGGAGAACCGCGCA	
	ATGGTAAGGAGAAAAGGATTTGGAATCCTGATAGGGGTC	
	TACGGAAGCTCTGTGATTTACATGGTTCAATTGCCGATCT	
	TTGGTGTCATAGATACACCTTGTTGGATCATCAAGGCAGC	
	TCCCTCTTGCTCAGAAAAAAACGGGAATTATGCTTGCCTC	
	CTAAGAGAGGATCAAGGGTGGTATTGTAAAAATGCAGGA	
	TCTACTGTTTACTACCCAAATGAAAAAGACTGCGAAACA	
	AGAGGTGATCATGTTTTTTGTGACACAGCAGCAGGGATC	
	AATGTTGCTGAGCAATCAAGAGAATGCAACATCAACATA	
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	CACCCTATAAGCATGGTTGCACTATCACCTCTCGGTGCTT	
	TGGTGGCTTGCTATAAAGGGGTAAGCTGCTCGATTGGCA	
	GCAATTGGGT	
	TGGAATCATCAAACAATTACCCAAAGGCTGCTCATACAT	
	AACCAACCAGGATGCAGACACTGTAACAATTGACAATAC	
	CGTGTATCAACTAAGCAAAGTTGAAGGTGAACAGCATGT	
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	CAAGTTTCCTGAGGATCAGTTCAATGTTGCGCTTGATCAA	
	GTCTTCGAAAGCATTGAGAACAGTCAGGCACTAGTGGAC	
	CAGTCAAACAAAATTCTAAACAGTGCAGAAAAAGGAAA	
	CACTGGTTTCATTATCGTAGTAATTTTGGTTGCTGTTCTTG	
	GTCTAACCATGATTTCAGTGAGCATCATCATCATAATCAA	
	GAAAACAAGGAAGCCCACAGGAGCACCTCCAGAGCTGA	
	ATGGTGTCACCAACGGCGGTTTCATACCACATAGTTA	
gb|KJ627414.1|: 3015-4634 Human metapneumo virus strain hMPV/*Homo sapiens*/PER/ CFI0497/2010/B, complete genome	ATGTCTTGGAAAGTGATGATTATCATTTCGTTACTCATAA	3
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	CATGTAGTACTATAACTGAAGGATATCTCAGTGTTTTAAG	
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	TAGCCACTGCAGTAAGAGAGCTGAAAGAATTTGTGAGCA	
	AAAACCTGACTAGTGCGATCAACAAGAACAAGTGTGACA	
	TTGCTGATTTGAAGATGGCTGTCAGCTTCAGTCAGTTCAA	
	CAGAAGATTCCTAAATGTTGTGCGGCAGTTTTCAGACAAT	
	GCAGGGATAACACCAGCAATATCATTGGACCTGATGAAT	
	GATGCTGAGCTGGCCAGAGCTGTATCATACATGCCAACA	
	TCTGCAGGACAGATAAAACTAATGTTAGAGAACCGTGCA	
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TABLE 2 -continued

Description	Sequence	SEQ ID NO:
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	CTAAGAGAGGATCAAGGGTGGTATTGTAAAAATGCAGGA	
	TCCACTGTTTACTACCCAAATGAAAAAGACTGCGAAACA	
	AGAGGTGATCATGTTTTTTGTGACACAGCAGCAGGGATC	
	AATGTTGCTGAGCAATCAAGAGAATGCAACATCAACATA	
	TCTACCACCAACTACCCATGCAAAGTCAGCACAGGAAGA	
	CACCCTATCAGCATGGTTGCACTATCACCTCTCGGTGCTT	
	TGGTAGCTTGCTACAAAGGGGTTAGCTGCTCGACTGGCA	
	GTAATCAGGTTGGAATAATCAAACAACTACCTAAAGGCT	
	GCTCATACATAACTAACCAGGACGCAGACACTGTAACAA	
	TTGACAACACTGTGTATCAACTAAGCAAAGTTGAGGGTG	
	AACAGCATGTAATAAAAGGGAGACCAGTTTCAAGCAGTT	
	TTGATCCAATCAGGTTTCCTGAGGATCAGTTCAATGTTGC	
	GCTTGATCAAGTCTTTGAAAGCATTGAAAACAGTCAAGC	
	ACTAGTGGACCAGTCAAACAAAATTCTGAACAGTGCAGA	
	AAAAGGAAACACTGGT	
	TTCATTATTGTAATAATTTTGATTGCTGTTCTTGGGTTAAC	
	CATGATTTCAGTGAGCATCATCATCATAATCAAAAAAAC	
	AAGGAAGCCCACAGGGGCACCTCCGGAGCTGAATGGTGT	
	TACCAACGGCGGTTTCATACCGCATAGTTAG	
gb|KJ723483.1|: 5586-7310 Human respiratory syncytial virus strain RSV A/*Homo sapiens*/USA/84I-215A-01/1984, complete genome	ATGGAGTTGCCAATCCTCAAAACAAATGCAATTACCACA	4
	ATCCTTGCTGCAGTCACACTCTGTTTCGCTTCCAGTCAAA	
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	TTAGCAAAGGCTATCTTAGTGCTCTAAGAACTGGTTGGTA	
	TACTAGTGTTATAACTATAGAATTAAGTAATATCAAGGA	
	AAATAAGTGTAATGGAACAGATGCTAAGGTAAAATTGAT	
	AAAACAAGAATTAGATAAATATAAAAATGCTGTAACAGA	
	ATTGCAGTTGCTCATGCAAAGCACACCAGCAGCCAACAA	
	TCGAGCCAGAAGAGAACTACCAAGGTTTATGAATTATAC	
	ACTCAATAATACCAAAAATACCAATGTAACATTAAGCAA	
	GAAAAGGAAAAGAAGATTTCTTGGCTTTTTGTTAGGTGTT	
	GGATCTGCAATCGCCAGTGGCATTGCTGTATCTAAGGTCC	
	TGCACCTAGAAGGGGAAGTGAACAAAATCAAAAGTGCTC	
	TACTATCCACAAACAAGGCTGTAGTCAGCTTATCAAATG	
	GAGTTAGTGTCTTAACCAGCAAAGTGTTAGACCTCAAAA	
	ACTATATAGATAAACAGTTGTTACCTATTGTGAACAAGC	
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	TCCAACAAAAGAACAACAGACTACTAGAGATTACCAGGG	
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	GACACAATGAACAGTTTAACATTACCAAGTGAAGTAAAT	
	CTCTGCAACATTGACATATTCAACCCCAAATATGATTGCA	
	AAATTATGACTTCAAAAACAGATGTAAGCAGCTCCGTTA	
	TCACATCTCTAGGAGCCATTGTGTCATGCTATGGCAAAAC	
	TAAATGTACAGCATCCAATAAAAATCGTGGGATCATAAA	
	GACATTTTCTAACGGGTGTGATTATGTATCAAATAAGGG	
	GGTGGATACTGTGTCTGTAGGTAATACATTATATTATGTA	
	AATAAGCAAGAAGGCAAAAGTCTCTATGTAAAAGGTGAA	
	CCAATAATAAATTTCTATGACCCATTAGTGTTCCCCTCTG	
	ATGAATTTGATGCATCAATATCTCAAGTCAATGAGAAGA	
	TTAACCAGAGCCTAGCATTTATTCGTAAATCCGATGAATT	
	ATTACATAATGTAAATGCTGGTAAATCCACCACAAATAT	
	CATGATAACTACTATAATTATAGTGATTATAGTAATATTG	
	TTATCATTAATTGCAGTTGGACTGCTCCTATACTGCAAGG	
	CCAGAAGCACACCAGTCACACTAAGTAAGGATCAACTGA	
	GTGGTATAAATAATATTGCATTTAGTAACTGA	
	hMPV mRNA Sequences	
gi|122891979|gb|EF051124.11 Human metapneumo virus isolate TN/92-4 fusion protein gene, complete genome	AUGAGCUGGAAGGUGGUGAUUAUCUUCAGCCUGCUGAU	57
	UACACCUCAACACGGCCUGAAGGAGAGCUACCUGGAAG	
	AGAGCUGCUCCACCAUCACCGAGGGCUACCUGAGCGUG	
	CUGCGGACCGGCUGGUACACCAACGUGUUCACCCUGGA	
	GGUGGGCGACGUGGAGAACCUGACCUGCAGCGACGGCC	
	CUAGCCUGAUCAAGACCGAGCUGGACCUGACCAAGAGC	
	GCUCUGAGAGAGCUGAAGACCGUGUCCGCCGACCAGCU	

TABLE 2 -continued

Description	Sequence	SEQ ID NO:
	GGCCAGAGAGGAACAGAUCGAGAACCCUCGGCAGAGCA	
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	CAUCAGACUGGAAAGCGAGGUGACAGCCAUCAACAAUG	
	CCCUGAAGAAGACCAACGAGGCCGUGAGCACCCUGGGC	
	AAUGGAGUGAGAGUGCUGGCCACAGCCGUGCGGGAGCU	
	GAAGGACUUCGUGAGCAAGAACCUGACCAGAGCCAUCA	
	ACAAGAACAAGUGCGACAUCGAUGACCUGAAGAUGGCC	
	GUGAGCUUCUCCCAGUUCAACAGACGGUUCCUGAACGU	
	GGUGAGACAGUUCUCCGACAACGCUGGAAUCACACCUG	
	CCAUUAGCCUGGACCUGAUGACCGACGCCGAGCUGGCU	
	AGAGCCGUGCCCAACAUGCCCACCAGCGCUGGCCAGAU	
	CAAGCUGAUGCUGGAGAACAGAGCCAUGGUGCGGAGAA	
	AGGGCUUCGGCAUCCUGAUUGGGGUGUAUGGAAGCUCC	
	GUGAUCUACAUGGUGCAGCUGCCCAUCUUCGGCGUGAU	
	CGACACACCCUGCUGGAUCGUGAAGGCCGCUCCUAGCU	
	GCUCCGAGAAGAAAGGAAACUAUGCCUGUCUGCUGAGA	
	GAGGACCAGGGCUGGUACUGCCAGAACGCCGGAAGCAC	
	AGUGUACUAUCCCAACGAGAAGGACUGCGAGACCAGAG	
	GCGACCACGUGUUCUGCGACACCGCUGCCGGAAUCAAC	
	GUGGCCGAGCAGAGCAAGGAGUGCAACAUCAACAUCAG	
	CACAACCAACUACCCCUGCAAGGUGAGCACCGGACGGC	
	ACCCCAUCAGCAUGGUGGCUCUGAGCCCUCUGGGCGCU	
	CUGGUGGCCUGCUAUAAGGGCGUGUCCUGUAGCAUCGG	
	CAGCAAUCGGGUGGGCAUCAUCAAGCAGCUGAACAAGG	
	GAUGCUCCUACAUCACCAACCAGGACGCCGACACCGUG	
	ACCAUCGACAACACCGUGUACCAGCUGAGCAAGGUGGA	
	GGGCGAGCAGCACGUGAUCAAGGGCAGACCCGUGAGCU	
	CCAGCUUCGACCCCAUCAAGUUCCCUGAGGACCAGUUC	
	AACGUGGCCCUGGACCAGGUGUUUGAGAACAUCGAGAA	
	CAGCCAGGCCCUGGUGGACCAGAGCAACAGAAUCCUGU	
	CCAGCGCUGAGAAGGGCAACACCGGCUUCAUCAUUGUG	
	AUCAUUCUGAUCGCCGUGCUGGGCAGCUCCAUGAUCCU	
	GGUGAGCAUCUUCAUCAUUAUCAAGAAGACCAAGAAAC	
	CCACCGGAGCCCCUCCUGAGCUGAGCGGCGUGACCAAC	
	AAUGGCUUCAUUCCCCACAACUGA	
gb|AY525843.1|: 3065-4684 Human metapneumo virus isolate NL/1/99, complete genome	AUGUCUUGGAAAGUGAUGAUCAUCAUUUCGUUACUCAU	58
	AACACCCCAGCACGGGCUAAAGGAGAGUUAUUUGGAAG	
	AAUCAUGUAGUACUAUAACUGAGGGAUACCUCAGUGUU	
	UUAAGAACAGGCUGGUACACUAAUGUCUUCACAUUAGA	
	AGUUGGUGAUGUUGAAAAUCUUACAUGUACUGAUGGA	
	CCUAGCUUAAUCAAAACAGAACUUGAUCUAACAAAAAG	
	UGCUUUAAGGGAACUCAAAACAGUCUCUGCUGAUCAGU	
	UGGCGAGAGAGGAGCAAAUUGAAAAUCCCAGACAAUCA	
	AGAUUUGUCUUAGGUGCGAUAGCUCUCGGAGUUGCUAC	
	AGCAGCAGCAGUCACAGCAGGCAUUGCAAUAGCCAAAA	
	CCAUAAGGCUUGAGAGUGAGGUGAAUGCAAUUAAAGG	
	UGCUCUCAAACAAACUAAUGAAGCAGUAUCCACAUUAG	
	GGAAUGGUGUGCGGGUCCUAGCCACUGCAGUGAGAGAG	
	CUAAAAGAAUUUGUGAGCAAAAACCUGACUAGUGCAAU	
	CAACAGGAACAAAUGUGACAUUGCUGAUCUGAAGAUGG	
	CUGUCAGCUUCAGUCAAUUCAACAGAAGAUUUCUAAAU	
	GUUGUGCGGCAGUUUUCAGACAAUGCAGGGAUAACACC	
	AGCAAUAUCAUUGGACCUGAUGACUGAUGCUGAGUUGG	
	CCAGAGCUGUAUCAUACAUGCCAACAUCUGCAGGGCAG	
	AUAAAACUGAUGUUGGAGAACCGCGCAAUGGUAAGGAG	
	AAAAGGAUUUGGAAUCCUGAUAGGGGUCUACGGAAGCU	
	CUGUGAUUUACAUGGUUCAAUUGCCGAUCUUUGGUGUC	
	AUAGAUACACCUUGUUGGAUCAUCAAGGCAGCUCCCUC	
	UUGCUCAGAAAAAAACGGGAAUUAUGCUUGCCUCCUAA	
	GAGAGGAUCAAGGGUGGUAUUGUAAAAAUGCAGGAUC	
	UACUGUUUACUACCCAAAUGAAAAAGACUGCGAAACAA	
	GAGGUGAUCAUGUUUUUUGUGACACAGCAGCAGGGAUC	
	AAUGUUGCUGAGCAAUCAAGAGAAUGCAACAUCAACAU	
	AUCUACUACCAACUACCCAUGCAAAGUCAGCACAGGAA	
	GACACCCUAUAAGCAUGGUUGCACUAUCACCUCUCGGU	
	GCUUUGGUGGCUUGCUAUAAAGGGGUAAGCUGCUCGAU	
	UGGCAGCAAUUGGGU	
	UGGAAUCAUCAAACAAUUACCCAAAGGCUGCUCAUACA	
	UAACCAACCAGGAUGCAGACACUGUAACAAUUGACAAU	
	ACCGUGUAUCAACUAAGCAAAGUUGAAGGUGAACAGCA	
	UGUAAUAAAAGGGAGACCAGUUUCAAGCAGUUUUGAUC	
	CAAUCAAGUUUCCUGAGGAUCAGUUCAAUGUUGCGCUU	
	GAUCAAGUCUUCGAAAGCAUUGAGAACAGUCAGGCACU	
	AGUGGACCAGUCAAACAAAAUUCUAAACAGUGCAGAAA	

TABLE 2 -continued

Description	Sequence	SEQ ID NO:
	AAGGAAACACUGGUUUCAUUAUCGUAGUAAUUUUGGU	
	UGCUGUUCUUGGUCUAACCAUGAUUUCAGUGAGCAUCA	
	UCAUCAUAAUCAAGAAAACAAGGAAGCCCACAGGAGCA	
	CCUCCAGAGCUGAAUGGUGUCACCAACGGCGGUUUCAU	
	ACCACAUAGUUAG	
gb|KJ627414.1|: 3015-4634 Human metapneumo virus strain hMPV/*Homo sapiens*/PER/ CFI0497/2010/B, complete genome	AUGUCUUGGAAAGUGAUGAUUAUCAUUUCGUUACUCAU	59
	AACACCUCAGCAUGGACUAAAAGAAAGUUAUUUAGAAG	
	AAUCAUGUAGUACUAUAACUGAAGGAUAUCUCAGUGUU	
	UUAAGAACAGGUUGGUACACCAAUGUCUUUACAUUAGA	
	AGUUGGUGAUGUUGAAAAUCUUACAUGUACUGAUGGA	
	CCUAGCUUAAUCAAAACAGAACUUGACCUAACCAAAAG	
	UGCUUUAAGAGAACUCAAAACAGUUUCUGCUGAUCAGU	
	UAGCGAGAGAAGAACAAAUUGAAAAUCCCAGACAAUCA	
	AGGUUUGUCCUAGGUGCAAUAGCUCUUGGAGUUGCCAC	
	AGCAGCAGCAGUCACAGCAGGCAUUGCAAUAGCCAAAA	
	CUAUAAGGCUUGAGAGUGAAGUGAAUGCAAUCAAAGG	
	UGCUCUCAAAACAACCAAUGAGGCAGUAUCAACACUAG	
	GAAAUGGAGUGCGGGUCCUAGCCACUGCAGUAAGAGAG	
	CUGAAAGAAUUUGUGAGCAAAAACCUGACUAGUGCGAU	
	CAACAAGAACAAGUGUGACAUUGCUGAUUUGAAGAUGG	
	CUGUCAGCUUCAGUCAGUUCAACAGAAGAUUCCUAAAU	
	GUUGUGCGGCAGUUUUCAGACAAUGCAGGGAUAACACC	
	AGCAAUAUCAUUGGACCUGAUGAAUGAUGCUGAGCUGG	
	CCAGAGCUGUAUCAUACAUGCCAACAUCUGCAGGACAG	
	AUAAAACUAAUGUUAGAGAACCGUGCAAUGGUGAGGA	
	GAAAAGGAUUUGGAAUCUUGAUAGGGGUCUACGGAAG	
	CUCUGUGAUUUACAUGGUCCAGCUGCCGAUCUUUGGUG	
	UCAUAAAUACACCUUGUUGGAUAAUCAAGGCAGCUCCC	
	UCUUGUUCAGAAAAAGAUGGAAAUUAUGCUUGCCUCCU	
	AAGAGAGGAUCAAGGGUGGUAUUGUAAAAAUGCAGGA	
	UCCACUGUUUACUACCCAAAUGAAAAAGACUGCGAAAC	
	AAGAGGUGAUCAUGUUUUUUGUGACACAGCAGCAGGGA	
	UCAAUGUUGCUGAGCAAUCAAGAGAAUGCAACAUCAAC	
	AUAUCUACCACCAACUACCCAUGCAAAGUCAGCACAGG	
	AAGACACCCUAUCAGCAUGGUUGCACUAUCACCUCUCG	
	GUGCUUUGGUAGCUUGCUACAAAGGGGUUAGCUGCUCG	
	ACUGGCAGUAAUCAGGUUGGAAUAAUCAAACAACUACC	
	UAAAGGCUGCUCAUACAUAACUAACCAGGACGCAGACA	
	CUGUAACAAUUGACAACACUGUGUAUCAACUAAGCAAA	
	GUUGAGGGUGAACAGCAUGUAAUAAAAGGGAGACCAG	
	UUUCAAGCAGUUUUGAUCCAAUCAGGUUUCCUGAGGAU	
	CAGUUCAAUGUUGCGCUUGAUCAAGUCUUUGAAAGCAU	
	UGAAAACAGUCAAGCACUAGUGGACCAGUCAAACAAAA	
	UUCUGAACAGUGCAGAAAAAGGAAACACUGGU	
	UUCAUUAUUGUAAUAAUUUUGAUUGCUGUUCUUGGGU	
	UAACCAUGAUUUCAGUGAGCAUCAUCAUCAUAAUCAAA	
	AAAACAAGGAAGCCCACAGGGGCACCUCCGGAGCUGAA	
	UGGUGUUACCAACGGCGGUUUCAUACCGCAUAGUUAG	
gb|KJ723483.1|: 5586-7310 Human respiratory syncytial virus strain RSVA/*Homo sapiens*/USA/84I-215A-01/1984, complete genome	AUGGAGUUGCCAAUCCUCAAAACAAAUGCAAUUACCAC	60
	AAUCCUUGCUGCAGUCACACUCUGUUUCGCUUCCAGUC	
	AAAACAUCACUGAAGAAUUUUAUCAAUCAACAUGCAGU	
	GCAGUUAGCAAAGGCUAUCUUAGUGCUCUAAGAACUGG	
	UUGGUAUACUAGUGUUAUAACUAUAGAAUUAAGUAAU	
	AUCAAGGAAAAUAAGUGUAAUGGAACAGAUGCUAAGG	
	UAAAAUUGAUAAAACAAGAAUUAGAUAAAUAUAAAAA	
	UGCUGUAACAGAAUUGCAGUUGCUCAUGCAAAGCACAC	
	CAGCAGCCAACAAUCGAGCCAGAAGAGAACUACCAAGG	
	UUUAUGAAUUAUACACUCAAUAAUACCAAAAAUACCAA	
	UGUAACAUUAAGCAAGAAAAGGAAAAGAAGAUUUCUU	
	GGCUUUUUGUUAGGUGUUGGAUCUGCAAUCGCCAGUGG	
	CAUUGCUGUAUCUAAGGUCCUGCACCUAGAAGGGGAAG	
	UGAACAAAAUCAAAAGUGCUCUACUAUCCACAAACAAG	
	GCUGUAGUCAGCUUAUCAAAUGGAGUUAGUGUCUUAAC	
	CAGCAAAGUGUUAGACCUCAAAAACUAUAUAGAUAAAC	
	AGUUGUUACCUAUUGUGAACAAGCAAAGCUGCAGCAUA	
	UCAAACAUUGAAACUGUGAUAGAGUUCCAACAAAAGAA	
	CAACAGACUACUAGAGAUUACCAGGGAAUUUAGUGUUA	
	AUGCAGGUGUAACUACACCUGUAAGCACUUAUAUGUUA	
	ACUAAUAGUGAAUUAUUAUCAUUAAUCAAUGAUAUGCC	
	UAUAACAAAUGAUCAGAAAAAGUUAAUGUCCAACAAUG	
	UUCAAAUAGUUAGACAGCAAAGUUACUCUAUCAUGUCC	
	AUAAUAAAGGAGGAAGUCUUAGCAUAUGUAGUACAAU	
	UACCACUAUAUGGUGUAAUAGAUACACCCUGUUGGAAA	
	CUGCACACAUCCCCUCUAUGUACAACCAACACAAAGGA	

TABLE 2 -continued

Description	Sequence	SEQ ID NO:
	AGGGUCCAACAUCUGCUUAACAAGAACCGACAGAGGAU	
	GGUAUUGUGACAAUGCAGGAUCAGUAUCUUUCUUCCCA	
	CAAGCUGAAACAUGUAAAGUUCAAUCGAAUCGGGUAUU	
	UUGUGACACAAUGAACAGUUUAACAUUACCAAGUGAAG	
	UAAAUCUCUGCAACAUUGACAUAUUCAACCCCAAAUAU	
	GAUUGCAAAAUUAUGACUUCAAAAACAGAUGUAAGCAG	
	CUCCGUUAUCACAUCUCUAGGAGCCAUUGUGUCAUGCU	
	AUGGCAAAACUAAAUGUACAGCAUCCAAUAAAAAUCGU	
	GGGAUCAUAAAGACAUUUUCUAACGGGUGUGAUUAUG	
	UAUCAAAUAAGGGGGUGGAUACUGUGUCUGUAGGUAA	
	UACAUUAUAUUAUGUAAAUAAGCAAGAAGGCAAAAGU	
	CUCUAUGUAAAAGGUGAACCAAUAAUAAAUUUCUAUGA	
	CCCAUUAGUGUUCCCCUCUGAUGAAUUUGAUGCAUCAA	
	UAUCUCAAGUCAAUGAGAAGAUUAACCAGAGCCUAGCA	
	UUUAUUCGUAAAUCCGAUGAAUUAUUACAUAAUGUAA	
	AUGCUGGUAAAUCCACCACAAAUAUCAUGAUAACUACU	
	AUAAUUAUAGUGAUUAUAGUAAUAUUGUUAUCAUUAA	
	UUGCAGUUGGACUGCUCCUAUACUGCAAGGCCAGAAGC	
	ACACCAGUCACACUAAGUAAGGAUCAACUGAGUGGUAU	
	AAAUAAUAUUGCAUUUAGUAACUGA	

TABLE 3

hMPV Amino Acid Sequences

Description	Sequence	SEQ ID NO:
gi|122891979|gb| EF051124.1| Human metapneumo virus isolate TN/92-4 fusion protein gene, complete cds	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGW YTNVFTLEVGDVENLTCSDGPSLIKTELDLTKSALRELKTVS ADQLAREEQIENPRQSRFVLGAIALGVAAAAAVTAGVAIAK TIRLESEVTAINNALKKTNEAVSTLGNGVRVLATAVRELKD FVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRA MVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPS CSEKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRG DHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRHPISM VALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQF NVALDQVFENIENSQALVDQSNRILSSAEKGNTGFIIVIILIAV LGSSMILVSIFIIIKKTKKPTGAPPELSGVTNNGFIPHN	5
gb|AY525843.1|: 3065-4684 Human metapneumo virus isolate NL/1/99, complete cds	MSWKVMIIISLLITPQHGLKESYLEESCSTITEGYLSVLRTGW YTNVFTLEVGDVENLTCTDGPSLIKTELDLTKSALRELKTVS ADQLAREEQIENPRQSRFVLGAIALGVATAAAVTAGIAIAKT IRLESEVNAIKGALKQTNEAVSTLGNGVRVLATAVRELKEF VSKNLTSAINRNKCDIADLKMAVSFSQFNRRFLNVVRQFSD NAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRAM VRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCS EKNGNYACLLREDQGWYCKNAGSTVYYPNEKDCETRGDH VFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVA LSPLGALVACYKGVSCSIGSNWVGIIKQLPKGCSYITNQDAD TVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNV ALDQVFESIENSQALVDQSNKILNSAEKGNTGFIIVVILVAVL GLTMISVSIIIIIKKTRKPTGAPPELNGVTNGGFIPHS	6
gb|KJ627414.1|: 3015-4634 Human metapneumo virus strain hMPV/*Homo sapiens*/PER/CFI04 97/2010/B, complete cds	MSWKVMIIISLLITPQHGLKESYLEESCSTITEGYLSVLRTGW YTNVFTLEVGDVENLTCTDGPSLIKTELDLTKSALRELKTVS ADQLAREEQIENPRQSRFVLGAIALGVATAAAVTAGIAIAKT IRLESEVNAIKGALKTTNEAVSTLGNGVRVLATAVRELKEF VSKNLTSAINKNKCDIADLKMAVSFSQFNRRFLNVVRQFSD NAGITPAISLDLMNDAELARAVSYMPTSAGQIKLMLENRAM VRRKGFGILIGVYGSSVIYMVQLPIFGVINTPCWIIKAAPSCS EKDGNYACLLREDQGWYCKNAGSTVYYPNEKDCETRGDH VFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVA LSPLGALVACYKGVSCSTGSNQVGIIKQLPKGCSYITNQDAD TVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIRFPEDQFNV ALDQVFESIENSQALVDQSNKILNSAEKGNTGFIIVIILIAVLG LTMISVSIIIIIKKTRKPTGAPPELNGVTNGGFIPHS	7
gb|KJ723483.1|: 5586-7310 Human	MELPILKTNAITTILAAVTLCFASSQNITEEFYQSTCSAVSKG YLSALRTGWYTSVITIELSNIKENKCNGTDAKVKLIKQELDK	8

TABLE 3 -continued

hMPV Amino Acid Sequences

Description	Sequence	SEQ ID NO:
respiratory syncytial virus strain RSVA/*Homo sapiens*/USA/84I-215A-01/1984, complete cds	YKNAVTELQLLMQSTPAANNRARRELPRFMNYTLNNTKNT NVTLSKKRKRRFLGFLLGVGSAIASGIAVSKVLHLEGEVNKI KSALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQLLPIVN KQSCSISNIETVIEFQQKNNRLLEITREFSVNAGVTTPVSTYM LTNSELLSLINDMPITNDQKKLMSNNVQIVRQQSYSIMSIIKE EVLAYVVQLPLYGVIDTPCWKLHTSPLCTTNTKEGSNICLTR TDRGWYCDNAGSVSFFPQAETCKVQSNRVFCDTMNSLTLP SEVNLCNIDIFNPKYDCKIMTSKTDVSSSVITSLGAIVSCYGK TKCTASNKNRGIIKTFSNGCDYVSNKGVDTVSVGNTLYYVN KQEGKSLYVKGEPIINFYDPLVFPSDEFDASISQVNEKINQSL AFIRKSDELLHNVNAGKSTTNIMITTIIIVIIVILLSLIAVGLLL YCKARSTPVTLSKDQLSGINNIAFSN	

TABLE 4

hMPV NCBI Accession Numbers (Amino Acid Sequences)

Virus	GenBank Accession
F [Human metapneumovirus] [Human metapneumovirus]	AEK26895.1
fusion glycoprotein [Human metapneumovirus]	ACJ53565.1
fusion glycoprotein [Human metapneumovirus]	ACJ53566.1
fusion glycoprotein [Human metapneumovirus]	ACJ53569.1
fusion protein [Human metapneumovirus]	AEZ52347.1
fusion glycoprotein [Human metapneumovirus]	ACJ53574.1
fusion glycoprotein [Human metapneumovirus]	AHV79473.1
fusion glycoprotein [Human metapneumovirus]	ACJ53570.1
fusion glycoprotein [Human metapneumovirus]	ACJ53567.1
fusion protein [Human metapneumovirus]	AAS22125.1
fusion glycoprotein [Human metapneumovirus]	AHV79795.1
fusion glycoprotein [Human metapneumovirus]	AHV79455.1
fusion glycoprotein [Human metapneumovirus]	ACJ53568.1
fusion protein [Human metapneumovirus]	AAS22109.1
fusion glycoprotein [Human metapneumovirus]	AGU68417.1
fusion glycoprotein [Human metapneumovirus]	AGJ74228.1
fusion glycoprotein [Human metapneumovirus]	ACJ53575.1
fusion protein [Human metapneumovirus]	AAU25820.1
fusion glycoprotein [Human metapneumovirus]	AGU68377.1
fusion glycoprotein [Human metapneumovirus]	AGU68371.1
fusion glycoprotein [Human metapneumovirus]	AGJ74087.1
fusion glycoprotein [Human metapneumovirus]	ACJ53560.1
fusion glycoprotein [Human metapneumovirus]	AHV79858.1
fusion glycoprotein [Human metapneumovirus]	ACJ53577.1
fusion protein [Human metapneumovirus]	AAS22085.1
fusion protein [Human metapneumovirus]	AEZ52348.1
fusion glycoprotein [Human metapneumovirus]	AGJ74044.1
fusion glycoprotein [Human metapneumovirus]	ACJ53563.1
fusion glycoprotein precursor [Human metapneumovirus]	YP_012608.1
fusion glycoprotein [Human metapneumovirus]	AGJ74053.1
fusion protein [Human metapneumovirus]	BAM37562.1
fusion glycoprotein [Human metapneumovirus]	ACJ53561.1
fusion glycoprotein [Human metapneumovirus]	AGU68387.1
fusion [Human metapneumovirus]	AGL74060.1
fusion glycoprotein precursor [Human metapneumovirus]	AAV88364.1
fusion protein [Human metapneumovirus]	AAN52910.1
fusion protein [Human metapneumovirus]	AAN52915.1
fusion protein [Human metapneumovirus]	BAM37564.1
fusion glycoprotein precursor [Human metapneumovirus]	BAH59618.1
fusion protein [Human metapneumovirus]	AAQ90144.1
fusion glycoprotein [Human metapneumovirus]	AHV79446.1
fusion protein [Human metapneumovirus]	AEL87260.1
fusion glycoprotein [Human metapneumovirus]	AHV79867.1
fusion protein [Human metapneumovirus]	ABQ66027.2
fusion glycoprotein [Human metapneumovirus]	ACJ53621.1
fusion protein [Human metapneumovirus]	AAN52911.1
fusion glycoprotein [Human metapneumovirus]	AHV79536.1
fusion glycoprotein [Human metapneumovirus]	AGU68411.1
fusion protein [Human metapneumovirus]	AEZ52346.1
fusion protein [Human metapneumovirus]	AAN52913.1
fusion protein [Human metapneumovirus]	AAN52908.1
fusion glycoprotein [Human metapneumovirus]	ACJ53553.1

TABLE 4-continued

hMPV NCBI Accession Numbers (Amino Acid Sequences)

Virus	GenBank Accession
fusion glycoprotein [Human metapneumovirus]	AIY25727.1
fusion protein [Human metapneumovirus]	ABM67072.1
fusion protein [Human metapneumovirus]	AEZ52361.1
fusion protein [Human metapneumovirus]	AAS22093.1
fusion glycoprotein [Human metapneumovirus]	AGH27049.1
fusion protein [Human metapneumovirus]	AAK62968.2
fusion glycoprotein [Human metapneumovirus]	ACJ53556.1
fusion glycoprotein [Human metapneumovirus]	ACJ53620.1
fusion protein [Human metapneumovirus]	ABQ58820.1
F [Human metapneumovirus] [Human metapneumovirus]	AEK26886.1
fusion glycoprotein [Human metapneumovirus]	ACJ53619.1
fusion glycoprotein [Human metapneumovirus]	ACJ53555.1
fusion [Human metapneumovirus]	AGL74057.1
fusion protein [Human metapneumovirus]	ABD27850.1
fusion protein [Human metapneumovirus]	AEZ52349.1
fusion protein [Human metapneumovirus]	ABD27848.1
fusion protein [Human metapneumovirus]	ABD27846.1
fusion protein [Human metapneumovirus]	ABQ66021.1
fusion protein [Human metapneumovirus]	AFM57710.1
fusion protein [Human metapneumovirus]	AFM57709.1
fusion protein [Human metapneumovirus]	ABH05968.1
fusion protein [Human metapneumovirus]	AEZ52350.1
fusion protein [Human metapneumovirus]	AFM57712.1
fusion protein [Human metapneumovirus]	AEZ52364.1
fusion protein [Human metapneumovirus]	AAN52912.1
fusion protein [Human metapneumovirus]	AEZ52363.1
fusion [Human metapneumovirus]	AGL74059.1
fusion glycoprotein [Human metapneumovirus]	ACJ53583.1
fusion protein [Human metapneumovirus]	AEZ52356.1
fusion protein [Human metapneumovirus]	AEZ52353.1
fusion glycoprotein [Human metapneumovirus]	ACJ53581.1
fusion glycoprotein [Human metapneumovirus]	ACJ53578.1
fusion protein [Human metapneumovirus]	AAS22117.1
fusion protein [Human metapneumovirus]	BAN75965.1
fusion protein [Human metapneumovirus]	AGF92105.1
fusion protein [Human metapneumovirus]	AAS22077.1
fusion protein [Human metapneumovirus]	AAN52909.1
fusion glycoprotein [Human metapneumovirus]	ACJ53586.1
fusion protein [Human metapneumovirus]	AAQ90145.1
fusion glycoprotein [Human metapneumovirus]	AGT75042.1
fusion [Human metapneumovirus]	AGL74058.1
fusion protein [Human metapneumovirus]	AEL87263.1
fusion glycoprotein [Human metapneumovirus]	AGH27057.1
fusion glycoprotein [Human metapneumovirus]	AHV79491.1
F [Human metapneumovirus] [Human metapneumovirus]	AEK26906.1
fusion glycoprotein [Human metapneumovirus]	ACJ53580.1
fusion protein [Human metapneumovirus]	AEZ52354.1
fusion protein [Human metapneumovirus]	AAN52914.1
G [Human metapneumovirus] [Human metapneumovirus]	AEK26901.1
glycoprotein [Human metapneumovirus]	AFI56738.1
glycoprotein [Human metapneumovirus]	AFI56739.1
glycoprotein [Human metapneumovirus]	AFI56745.1
G protein [Human metapneumovirus]	AAQ62718.1
G protein [Human metapneumovirus]	AAQ62719.1
attachment glycoprotein G [Human metapneumovirus]	AGH27104.1
G protein [Human metapneumovirus]	AAQ62729.1
G protein [Human metapneumovirus]	AAQ62728.1
glycoprotein [Human metapneumovirus]	AFI56753.1
glycoprotein [Human metapneumovirus]	AFI56746.1
glycoprotein [Human metapneumovirus]	AFI56750.1
glycoprotein [Human metapneumovirus]	AFI56747.1
G protein [Human metapneumovirus]	AAQ62721.1
glycoprotein [Human metapneumovirus]	AAT46573.1
glycoprotein [Human metapneumovirus]	AFI56748.1
glycoprotein [Human metapneumovirus]	AFI56736.1
glycoprotein [Human metapneumovirus]	AFI56749.1
attachment glycoprotein G [Human metapneumovirus]	AGH27131.1
attachment glycoprotein G [Human metapneumovirus]	AHV79558.1
glycoprotein [Human metapneumovirus]	AFI56740.1
glycoprotein [Human metapneumovirus]	AFI56741.1
glycoprotein [Human metapneumovirus]	AFI56744.1
attachment glycoprotein G [Human metapneumovirus]	AHV79790.1
attachment glycoprotein G [Human metapneumovirus]	AGH27122.1
attachment glycoprotein G [Human metapneumovirus]	AHV79763.1
attachment glycoprotein G [Human metapneumovirus]	AGZ48849.1
glycoprotein [Human metapneumovirus]	AFI56743.1

TABLE 4-continued

hMPV NCBI Accession Numbers (Amino Acid Sequences)

Virus	GenBank Accession
attachment glycoprotein G [Human metapneumovirus]	AHV79450.1
glycoprotein [Human metapneumovirus]	AFI56751.1
attachment glycoprotein [Human metapneumovirus]	AAS48482.1
attachment glycoprotein G [Human metapneumovirus]	AHV79889.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43050.1
glycoprotein [Human metapneumovirus]	AFI56754.1
attachment glycoprotein G [Human metapneumovirus]	AHV79601.1
glycoprotein [Human metapneumovirus]	AFI56752.1
attachment glycoprotein G [Human metapneumovirus]	AHV79871.1
G protein [Human metapneumovirus]	AEZ68099.1
attachment glycoprotein G [Human metapneumovirus]	AHV79817.1
attachment glycoprotein G [Human metapneumovirus]	AHV79943.1
attachment glycoprotein G [Human metapneumovirus]	BAN75968.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43045.1
attachment glycoprotein G [Human metapneumovirus]	AHV79628.1
attachment glycoprotein [Human metapneumovirus]	AFK49783.1
G protein [Human metapneumovirus]	AAQ62723.1
attachment glycoprotein [Human metapneumovirus]	ABD27839.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43046.1
G protein [Human metapneumovirus]	AAQ62717.1
glycoprotein [Human metapneumovirus]	AFI56742.1
attachment protein [Human metapneumovirus]	ABQ44522.1
glycoprotein [Human metapneumovirus]	AFI56735.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43065.1
G protein [Human metapneumovirus]	AAQ62724.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43075.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43062.1
glycoprotein [Human metapneumovirus]	AAT46579.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43064.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43054.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43042.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43078.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43067.1
G protein [Human metapneumovirus]	AAQ62722.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43063.1
glycoprotein [Human metapneumovirus]	AAT46571.1
glycoprotein [Human metapneumovirus]	AAT46578.1
attachment glycoprotein G [Human metapneumovirus]	AGJ74232.1
glycoprotein [Human metapneumovirus]	AAT46580.1
glycoprotein [Human metapneumovirus]	AAT46574.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43061.1
attachment glycoprotein [Human metapneumovirus]	AFK49791.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43047.1
glycoprotein [Human metapneumovirus]	ABC26386.1
attachment glycoprotein [Human metapneumovirus]	AAS48466.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43048.1
attachment glycoprotein G [Human metapneumovirus]	AGH27140.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43049.1
attachment glycoprotein G [Human metapneumovirus]	AGJ74082.1
attachment glycoprotein G [Human metapneumovirus]	AHV79442.1
attachment glycoprotein G [Human metapneumovirus]	AGJ74091.1
attachment glycoprotein G [Human metapneumovirus]	AHV79477.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43056.1
attachment protein [Human metapneumovirus]	ABQ44523.1
attachment glycoprotein G [Human metapneumovirus]	BAH59622.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43070.1
glycoprotein [Human metapneumovirus]	AAT46585.1
attachment glycoprotein G [Human metapneumovirus]	AGU68409.1
attachment glycoprotein G [Human metapneumovirus]	AGJ74223.1
attachment glycoprotein [Human metapneumovirus]	AAS22129.1
attachment glycoprotein G [Human metapneumovirus]	AGJ74048.1
G protein [Human metapneumovirus]	AAQ62725.1
glycoprotein [Human metapneumovirus]	ABC26384.1
attachment protein [Human metapneumovirus]	ABQ44525.1
attachment glycoprotein G [Human metapneumovirus]	YP_012612.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43071.1
attachment glycoprotein G [Human metapneumovirus]	AGJ74162.1
attachment glycoprotein G [Human metapneumovirus]	AGH27095.1
attachment glycoprotein G [Human metapneumovirus]	AHV79531.1
G protein [Human metapneumovirus]	AAQ62726.1
attachment glycoprotein [Human metapneumovirus]	AAS48465.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43058.1
P [Human metapneumovirus] [Human metapneumovirus]	AEK26894.1
phosphoprotein [Human metapneumovirus]	AHV79631.1
phosphoprotein [Human metapneumovirus]	AHV79901.1
phosphoprotein [Human metapneumovirus]	AHV79570.1

TABLE 4-continued

hMPV NCBI Accession Numbers (Amino Acid Sequences)

Virus	GenBank Accession
phosphoprotein [Human metapneumovirus]	AGJ74076.1
phosphoprotein [Human metapneumovirus]	AAS22123.1
phosphoprotein [Human metapneumovirus]	ABB16895.1
phosphoprotein [Human metapneumovirus]	AHV79579.1
phosphoprotein [Human metapneumovirus]	AGJ74244.1
phosphoprotein [Human metapneumovirus]	AHV79856.1
phosphoprotein [Human metapneumovirus]	ACJ70113.1
phosphoprotein [Human metapneumovirus]	AGZ48843.1
phosphoprotein [Human metapneumovirus]	AHV79498.1
phosphoprotein [Human metapneumovirus]	AHV79480.1
phosphoprotein [Human metapneumovirus]	ABQ43382.1
phosphoprotein [Human metapneumovirus]	AAS22107.1
phosphoprotein [Human metapneumovirus]	ABB16898.1
phosphoprotein [Human metapneumovirus]	AGH27134.1
phosphoprotein [Human metapneumovirus]	ABB16899.1
phosphoprotein [Human metapneumovirus]	AGH27098.1
phosphoprotein [Human metapneumovirus]	AAN52866.1
phosphoprotein [Human metapneumovirus]	AAS22083.1
phosphoprotein [Human metapneumovirus]	YP_012606.1
phosphoprotein [Human metapneumovirus]	AHV79973.1
phosphoprotein [Human metapneumovirus]	AHV79462.1
phosphoprotein [Human metapneumovirus]	AGJ74042.1
phosphoprotein [Human metapneumovirus]	AAV88362.1
P [Human metapneumovirus] [Human metapneumovirus]	AIL23591.1
phosphoprotein [Human metapneumovirus]	AHV79453.1
phosphoprotein [Human metapneumovirus]	AGJ74261.1
phosphoprotein [Human metapneumovirus]	AGH27116.1
phosphoprotein [Human metapneumovirus]	ABB16444.1
phosphoprotein [Human metapneumovirus]	ABB16445.1
phosphoprotein [Human metapneumovirus]	AHV79507.1
phosphoprotein [Human metapneumovirus]	BAH59616.1
phosphoprotein [Human metapneumovirus]	ABB16443.1
phosphoprotein [Human metapneumovirus]	ABQ43388.1
phosphoprotein [Human metapneumovirus]	ABQ43389.1
phosphoprotein [Human metapneumovirus]	ABQ43395.1
phosphoprotein [Human metapneumovirus]	ABQ43385.1
phosphoprotein [Human metapneumovirus]	AAP84042.1
phosphoprotein [Human metapneumovirus]	AAN52868.1
phosphoprotein [Human metapneumovirus]	AAP84041.1
phosphoprotein [Human metapneumovirus]	AGH27080.1
phosphoprotein [Human metapneumovirus]	ABQ43387.1
phosphoprotein [Human metapneumovirus]	AAS22099.1
phosphoprotein [Human metapneumovirus]	ABB16896.1
phosphoprotein [Human metapneumovirus]	AGJ74094.1
phosphoprotein [Human metapneumovirus]	AEZ68089.1
phosphoprotein [Human metapneumovirus]	ABK97002.1
phosphoprotein [Human metapneumovirus]	AAP13486.1
phosphoprotein [Human metapneumovirus]	AHV79444.1
phosphoprotein [Human metapneumovirus]	AHV79865.1
phosphoprotein [Human metapneumovirus]	AGJ74226.1
phosphoprotein [Human metapneumovirus]	ABQ43383.1
phosphoprotein [Human metapneumovirus]	AAN52863.1
phosphoprotein [Human metapneumovirus]	AHV79775.1
phosphoprotein [Human metapneumovirus]	AEZ68094.1
phosphoprotein [Human metapneumovirus]	AHV79883.1
phosphoprotein [Human metapneumovirus]	AEZ68092.1
phosphoprotein [Human metapneumovirus]	ABQ43390.1
phosphoprotein [Human metapneumovirus]	ABQ43386.1
phosphoprotein [Human metapneumovirus]	ABQ43391.1
phosphoprotein [Human metapneumovirus]	ACS16062.1
phosphoprotein [Human metapneumovirus]	AEZ68090.1
phosphoprotein [Human metapneumovirus]	AAK62967.1
phosphoprotein [Human metapneumovirus]	AEZ68093.1
phosphoprotein [Human metapneumovirus]	AEZ68088.1
phosphoprotein [Human metapneumovirus]	ABQ43392.1
phosphoprotein [Human metapneumovirus]	ABQ43393.1
phosphoprotein [Human metapneumovirus]	ABQ43384.1
phosphoprotein [Human metapneumovirus]	ABQ43394.1
phosphoprotein [Human metapneumovirus]	ABK96999.1
phosphoprotein [Human metapneumovirus]	AHV79489.1
phosphoprotein [Human metapneumovirus]	AGJ74235.1
phosphoprotein [Human metapneumovirus]	AAS22075.1
phosphoprotein [Human metapneumovirus]	AAS22115.1
phosphoprotein [Human metapneumovirus]	AII17601.1
phosphoprotein [Human metapneumovirus]	ABK97000.1
phosphoprotein [Human metapneumovirus]	AHV79561.1

TABLE 4-continued

hMPV NCBI Accession Numbers (Amino Acid Sequences)

Virus	GenBank Accession
phosphoprotein [Human metapneumovirus]	AGT75040.1
phosphoprotein [Human metapneumovirus]	AAN52864.1
phosphoprotein [Human metapneumovirus]	ABK97001.1
phosphoprotein [Human metapneumovirus]	AGT74979.1
phosphoprotein [Human metapneumovirus]	AHV79955.1
phosphoprotein [Human metapneumovirus]	AGH27055.1
phosphoprotein [Human metapneumovirus]	AAV88361.1
phosphoprotein [Human metapneumovirus]	ABQ43397.1
phosphoprotein [Human metapneumovirus]	AGJ74173.1
P [Human metapneumovirus] [Human metapneumovirus]	AEK26904.1
phosphoprotein [Human metapneumovirus]	ACJ70104.1
phosphoprotein [Human metapneumovirus]	ABK97003.1
phosphoprotein [Human metapneumovirus]	AGT74955.1
phosphoprotein [Human metapneumovirus]	AAN52856.1
phosphoprotein [Human metapneumovirus]	AAN52862.1
phosphoprotein [Human metapneumovirus]	AGJ74138.1
phosphoprotein [Human metapneumovirus]	AHV79613.1
phosphoprotein [Human metapneumovirus]	AGJ74060.1
phosphoprotein [Human metapneumovirus]	AAQ67684.1
phosphoprotein [Human metapneumovirus]	AEA02278.1
N [Human metapneumovirus] [Human metapneumovirus]	AEK26899.1
nucleoprotein [Human metapneumovirus]	ACS16061.1
nucleoprotein [Human metapneumovirus]	AAS88425.1
nucleoprotein [Human metapneumovirus]	YP_012605.1
nucleoprotein [Human metapneumovirus]	AHV79882.1
nucleoprotein [Human metapneumovirus]	AHV79774.1
nucleocapsid protein [Human metapneumovirus]	AAN52886.1
nucleoprotein [Human metapneumovirus]	AAS22082.1
nucleoprotein [Human metapneumovirus]	AHV79864.1
nucleoprotein [Human metapneumovirus]	AHV79828.1
nucleoprotein [Human metapneumovirus]	AGJ74084.1
nucleocapsid protein [Human metapneumovirus]	AAN52888.1
N [Human metapneumovirus] [Human metapneumovirus]	AIL23590.1
nucleoprotein [Human metapneumovirus]	AAK62966.1
nucleoprotein [Human metapneumovirus]	AHV79972.1
nucleoprotein [Human metapneumovirus]	AHV79470.1
nucleoprotein [Human metapneumovirus]	AHV79452.1
nucleoprotein [Human metapneumovirus]	AGJ74243.1
nucleoprotein [Human metapneumovirus]	AHV79533.1
nucleoprotein [Human metapneumovirus]	AGJ74181.1
nucleoprotein [Human metapneumovirus]	AHV79497.1
nucleoprotein [Human metapneumovirus]	AHV79702.1
nucleoprotein [Human metapneumovirus]	AHV79648.1
nucleoprotein [Human metapneumovirus]	AHV79435.1
putative nucleoprotein [Human metapneumovirus]	AGJ74260.1
nucleocapsid protein [Human metapneumovirus]	AAN52887.1
nucleoprotein [Human metapneumovirus]	AGU68386.1
nucleocapsid protein [Human metapneumovirus]	AAN52899.1
nucleoprotein [Human metapneumovirus]	AAR17673.1
nucleocapsid protein [Human metapneumovirus]	AAN52898.1
nucleoprotein [Human metapneumovirus]	AEA02277.1
nucleoprotein [Human metapneumovirus]	AHV79612.1
nucleoprotein [Human metapneumovirus]	AGU68416.1
nucleoprotein [Human metapneumovirus]	AGU68408.1
nucleoprotein [Human metapneumovirus]	AGU68370.1
nucleoprotein [Human metapneumovirus]	AAQ67683.1
nucleoprotein [Human metapneumovirus]	AGJ74137.1
nucleoprotein [Human metapneumovirus]	AGU68344.1
nucleocapsid protein [Human metapneumovirus]	ABK96997.1
nucleoprotein [Human metapneumovirus]	AGU68413.1
nucleocapsid protein [Human metapneumovirus]	AAN52891.1
nucleoprotein [Human metapneumovirus]	AGU68360.1
nucleoprotein [Human metapneumovirus]	AGU68353.1
nucleocapsid protein [Human metapneumovirus]	ABK96996.1
nucleoprotein [Human metapneumovirus]	AAR17666.1
N [Human metapneumovirus] [Human metapneumovirus]	AEK26903.1
nucleoprotein [Human metapneumovirus]	AGT75039.1
nucleoprotein [Human metapneumovirus]	AGU68410.1
nucleoprotein [Human metapneumovirus]	AAS22074.1
nucleoprotein [Human metapneumovirus]	AHV79560.1
nucleoprotein [Human metapneumovirus]	AGT74978.1
nucleoprotein [Human metapneumovirus]	AGJ74128.1
nucleoprotein [Human metapneumovirus]	AAR17663.1
nucleoprotein [Human metapneumovirus]	AAR17662.1
nucleoprotein [Human metapneumovirus]	AAR17664.1
nucleoprotein [Human metapneumovirus]	AAR17657.1

TABLE 4-continued

hMPV NCBI Accession Numbers (Amino Acid Sequences)

Virus	GenBank Accession
nucleoprotein [Human metapneumovirus]	AAR17659.1
nucleoprotein [Human metapneumovirus]	AAR17661.1
nucleoprotein [Human metapneumovirus]	AGU68352.1
nucleoprotein [Human metapneumovirus]	AGU68373.1
nucleoprotein [Human metapneumovirus]	AGU68376.1
nucleoprotein [Human metapneumovirus]	AGU68342.1
nucleoprotein [Human metapneumovirus]	AGU68365.1
nucleoprotein [Human metapneumovirus]	AGU68363.1
nucleoprotein [Human metapneumovirus]	AGU68398.1
nucleoprotein [Human metapneumovirus]	AGU68348.1
nucleoprotein [Human metapneumovirus]	AGU68354.1
nucleoprotein [Human metapneumovirus]	AGU68391.1
nucleoprotein [Human metapneumovirus]	AGU68389.1
nucleoprotein [Human metapneumovirus]	AGU68399.1
nucleoprotein [Human metapneumovirus]	AGU68337.1
nucleoprotein [Human metapneumovirus]	AAR17660.1
nucleoprotein [Human metapneumovirus]	AAR17667.1
nucleoprotein [Human metapneumovirus]	AGU68402.1
nucleoprotein [Avian metapneumovirus type C]	CDN30025.1
nucleoprotein [Avian metapneumovirus]	AGZ87947.1
Nucleoprotein [Avian metapneumovirus type C]	CAL25113.1
nucleocapsid protein [Avian metapneumovirus]	ABO42286.1
nucleocapsid protein [Avian metapneumovirus]	AAK38430.1
nucleocapsid protein [Avian metapneumovirus]	AAK54155.1
nucleocapsid protein [Avian metapneumovirus]	AAK38426.1
nucleocapsid protein [Avian metapneumovirus]	AAK38425.1
nucleocapsid protein [Avian metapneumovirus]	AAK38424.1
nucleocapsid protein [Avian metapneumovirus]	AAF05909.1
nucleocapsid protein [Avian metapneumovirus]	AAK38435.1
nucleocapsid protein [Avian metapneumovirus]	AAK38428.1
nucleoprotein [Human metapneumovirus]	AAR17669.1
nucleocapsid protein [Avian metapneumovirus]	AAK38429.1
nucleocapsid protein [Avian metapneumovirus]	AAK38427.1
nucleocapsid protein [Avian metapneumovirus]	AAK38423.1
nucleocapsid protein [Avian metapneumovirus]	AAK38434.1
nucleoprotein [Human metapneumovirus]	AGU68338.1
nucleoprotein [Avian metapneumovirus]	YP_443837.1
nucleoprotein [Human metapneumovirus]	AGU68384.1
nucleocapsid protein [Avian metapneumovirus]	AAK38431.1
nucleoprotein [Human metapneumovirus]	AGU68405.1
nucleoprotein [Human metapneumovirus]	AGU68382.1
nucleoprotein [Human metapneumovirus]	AGU68395.1
nucleocapsid [Human metapneumovirus]	AAL35389.3
nucleoprotein [Human metapneumovirus]	AEZ68064.1

TABLE 5

Description	Sequence	SEQ ID NO:
	PIV3 Nucleic Acid Sequences	
>gb|KJ672601.1|: 4990-6609 Human parainfluenza virus 3 strain HPIV3/*Homo sapiens*/ PER/FLA4815/2008 [fusion glycoprotein F0]	ATGCCAATTTCAATACTGTTAATTATTACAACCATGATC ATGGCATCACACTGCCAAATAGACATCACAAAACTACA GCATGTAGGTGTATTGGTCAACAGTCCCAAAGGGATGA AGATATCACAAAACTTCGAAACAAGATATCTAATCCTGA GTCTCATACCAAAAATAGAAGATTCTAACTCTTGTGGTG ACCAACAGATCAAGCAATACAAGAGGTTATTGGATAGA CTGATCATTCCTTTATATGATGGACTAAGATTACAGAAG GATGTGATAGTGACTAATCAAGAATCCAATGAAAACAC TGATCCCAGAACAGAACGATTCTTTGGAGGGGTAATTGG AACTATTGCTCTAGGAGTAGCAACCTCAGCACAAATTAC AGCAGCAGTTGCTCTGGTTGAAGCCAAGCAGGCAAGAT CAGACATTGAAAAACTCAAGGAAGCAATCAGGGACACA AATAAAGCAGTGCAGTCAGTTCAGAGCTCTGTAGGAAA TTTGATAGTAGCAATTAAATCAGTCCAGGATTATGTCAA CAAAGAAATCGTGCCATCGATTGCGAGACTAGGTTGTG AAGCAGCAGGACTTCAGTTAGGGATTGCATTAACACAG CATTACTCAGAATTAACAAATATATTTGGTGATAACATA GGATCGTTACAAGAAAAAGGAATAAAATTACAAGGTAT AGCATCATTATACCGTACAAATATCACAGAAATATTCAC AACATCAACAGTTGACAAATATGATATTTATGATCTATT	9

TABLE 5 -continued

Description	Sequence	SEQ ID NO:
	ATTTACAGAATCAATAAAGGTGAGAGTTATAGATGTTGA TTTGAATGATTACTCAATAACCCTCCAAGTCAGACTCCC TTTATTGACCAGACTGCTGAACACTCAAATCTACAAAGT AGATTCCATATCATACAATATCCAAAATAGAGAATGGTA TATCCCTCTTCCCAGCCATATCATGACGAAAGGGGCATT TCTAGGTGGAGCAGATGTCAAAGAATGCATAGAAGCAT TCAGCAGTTATATATGCCCTTCTGATCCAGGATTTGTACT AAACCATGAAATGGAGAGCTGTCTATCAGGAAACATAT CCCAATGTCCAAGAACCACAGTCACATCAGACATAGTTC CTAGGTATGCATTTGTCAATGGAGGAGTGGTTGCGAATT GTATAACAACTACATGTACATGCAATGGTATCGGTAATA GAATCAACCAACCACCTGATCAAGGAGTCAAAATTATA ACACATAAAGAATGTAATACAATAGGTATCAACGGAAT GCTATTCAACACAAACAAAGAAGGAACTCTTGCATTCTA CACACCAGACGACATAACATTAAACAATTCTGTTGCACT TGATCCGATTGACATATCAATCGAGCTCAACAAGGCCAA ATCAGATCTTGAGGAATCAAAAGAATGGATAAGAAGGT CAAATCAAAAGCTAGATTCTATTGGAAGTTGGCATCAAT CTAGCACTACAATCATAGTTATTTTGATAATGATGATTA TATTGTTTATAATTAATATAACAATAATTACAATTGCAA TTAAGTATTACAGAATTCAAAAGAGAAATCGAGTGGAT CAAAATGATAAGCCGTATGTATTAACAAACAAG	
gi|612507167|gb| AHX22430.1| hemagglutinin- neuraminidase [Human parainfluenza virus 3]	ATGGAATACTGGAAGCACACCAACCACGGAAAGGATGC TGGTAATGAGCTGGAGACATCCACAGCCACTCATGGCA ACAAGCTCACCAACAAGATAACATATATATTGTGGACG ATAACCCTGGTGTTATTATCAATAGTCTTCATCATAGTG CTAACTAATTCCATCAAAAGTGAAAAGGCCCGCGAATC ATTGCTACAAGACATAAATAATGAGTTTATGGAAGTTAC AGAAAAGATCCAAGTGGCATCGGATAATACTAATGATC TAATACAGTCAGGAGTGAATACAAGGCTTCTTACAATTC AGAGTCATGTCCAGAATTATATACCAATATCATTGACAC AACAAATATCGGATCTTAGGAAATTCATTAGTGAAATTA CAATTAGAAATGATAATCAAGAAGTGCCACCACAAAGA ATAACACATGATGTGGGTATAAAACCTTTAAATCCAGAT GATTTCTGGAGATGCACGTCTGGTCTTCCATCTTTGATG AAAACTCCAAAAATAAGATTAATGCCGGGACCAGGATT ATTAGCTATGCCAACGACTGTTGATGGCTGTGTCAGAAC CCCGTCCTTAGTGATAAATGATCTGATTTATGCTTACAC CTCAAATCTAATTACTCGAGGTTGCCAGGATATAGGGAA ATCATATCAAGTATTACAGATAGGGATAATAACTGTAAA CTCAGACTTGGTACCTGACTTAAATCCTAGGATCTCTCA TACCTTCAACATAAATGACAATAGAAAGTCATGTTCTCT AGCACTCCTAAATACAGATGTATATCAACTGTGTTCAAC CCCAAAAGTTGATGAAAGATCAGATTATGCATCATCAG GCATAGAAGATATTGTACTTGATATTGTCAATTATGATG GCTCAATCTCGACAACAAGATTTAAGAATAATAATATAA GTTTTGATCAACCATATGCGGCATTATACCCATCTGTTG GACCAGGGATATACTACAAAGGCAAAATAATATTTCTC GGGTATGGAGGTCTTGAACATCCAATAAATGAGAATGC AATCTGCAACACAACTGGGTGTCCTGGGAAAACACAGA GAGACTGTAATCAAGCATCTCATAGTCCATGGTTTTCAG ATAGAAGGATGGTCAACTCTATAATTGTTGTTGACAAGG GCTTGAACTCAGTTCCAAAATTGAAGGTATGGACGATAT CTATGAGACAAAATTACTGGGGGTCAGAAGGAAGATTA CTTCTACTAGGTAACAAGATCTACATATACACAAGATCT ACAAGTTGGCACAGCAAGTTACAATTAGGAATAATTGA CATTACTGACTACAGTGATATAAGGATAAAATGGACAT GGCATAATGTGCTATCAAGACCAGGAAACAATGAATGT CCATGGGGACATTCATGTCCGGATGGATGTATAACGGG AGTATATACCGATGCATATCCACTCAATCCCACAGGAAG CATTGTATCATCTGTCATATTGGACTCACAAAAATCGAG AGTCAACCCAGTCATAACTTACTCAACAGCAACCGAAA GGGTAAACGAGCTGGCTATCCGAAACAAAACACTCTCA GCTGGGTACACAACAACAAGCTGCATTACACACTATAA CAAAGGGTATTGTTTTCATATAGTAGAAATAAATCATAA AAGCTTAAACACATTTCAACCCATGTTGTTCAAAACAGA GATTCCAAAAAGCTGCAGT	10
HPIV3_HN_Codon Optimized	ATGGAATACTGGAAGCACACCAACCACGGCAAGGACGC CGGCAACGAGCTGGAAACCAGCACAGCCACACACGGCA ACAAGCTGACCAACAAGATCACCTACATCCTGTGGACC ATCACCCTGGTGCTGCTGAGCATCGTGTTCATCATCGTG CTGACCAATAGCATCAAGAGCGAGAAGGCCAGAGAGAG CCTGCTGCAGGACATCAACAACGAGTTCATGGAAGTGA CCGAGAAGATCCAGGTGGCCAGCGACAACACCAACGAC	11

TABLE 5 -continued

Description	Sequence	SEQ ID NO:
	CTGATCCAGAGCGGCGTGAACACCCGGCTGCTGACCATC	
	CAGAGCCACGTGCAGAACTACATCCCCATCAGCCTGACC	
	CAGCAGATCAGCGACCTGCGGAAGTTCATCAGCGAGAT	
	CACCATCCGGAACGACAACCAGGAAGTGCCCCCCCAGA	
	GAATCACCCACGACGTGGGCATCAAGCCCCTGAACCCC	
	GACGATTTCTGGCGGTGTACAAGCGGCCTGCCCAGCCTG	
	ATGAAGACCCCCAAGATCCGGCTGATGCCTGGCCCTGG	
	ACTGCTGGCCATGCCTACCACAGTGGATGGCTGTGTGCG	
	GACCCCCAGCCTCGTGATCAACGATCTGATCTACGCCTA	
	CACCAGCAACCTGATCACCCGGGGCTGCCAGGATATCG	
	GCAAGAGCTACCAGGTGCTGCAGATCGGCATCATCACC	
	GTGAACTCCGACCTGGTGCCCGACCTGAACCCTCGGATC	
	AGCCACACCTTCAACATCAACGACAACAGAAAGAGCTG	
	CAGCCTGGCTCTGCTGAACACCGACGTGTACCAGCTGTG	
	CAGCACCCCCAAGGTGGACGAGAGAAGCGACTACGCCA	
	GCAGCGGCATCGAGGATATCGTGCTGGACATCGTGAAC	
	TACGACGGCAGCATCAGCACCACCCGGTTCAAGAACAA	
	CAACATCAGCTTCGACCAGCCCTACGCCGCCCTGTACCC	
	TTCTGTGGGCCCTGGCATCTACTACAAGGGCAAGATCAT	
	CTTCCTGGGCTACGGCGGCCTGGAACACCCCATCAACGA	
	GAACGCCATCTGCAACACCACCGGCTGCCCTGGCAAGA	
	CCCAGAGAGACTGCAATCAGGCCAGCCACAGCCCCTGG	
	TTCAGCGACCGCAGAATGGTCAACTCTATCATCGTGGTG	
	GACAAGGGCCTGAACAGCGTGCCCAAGCTGAAAGTGTG	
	GACAATCAGCATGCGCCAGAACTACTGGGGCAGCGAGG	
	GCAGACTTCTGCTGCTGGGAAACAAGATCTACATCTACA	
	CCCGGTCCACCAGCTGGCACAGCAAACTGCAGCTGGGA	
	ATCATCGACATCACCGACTACAGCGACATCCGGATCAA	
	GTGGACCTGGCACAACGTGCTGAGCAGACCCGGCAACA	
	ATGAGTGCCCTTGGGGCCACAGCTGCCCCGATGGATGTA	
	TCACCGGCGTGTACACCGACGCCTACCCCCTGAATCCTA	
	CCGGCTCCATCGTGTCCAGCGTGATCCTGGACAGCCAGA	
	AAAGCAGAGTGAACCCCGTGATCACATACAGCACCGCC	
	ACCGAGAGAGTGAACGAACTGGCCATCAGAAACAAGAC	
	CCTGAGCGCCGGCTACACCACCACAAGCTGCATCACAC	
	ACTACAACAAGGGCTACTGCTTCCACATCGTGGAAATCA	
	ACCACAAGTCCCTGAACACCTTCCAGCCCATGCTGTTCA	
	AGACCGAGATCCCCAAGAGCTGCTCC	
HPIV3_F_Codon Optimized	ATGCCCATCAGCATCCTGCTGATCATCACCACAATGATC	12
	ATGGCCAGCCACTGCCAGATCGACATCACCAAGCTGCA	
	GCACGTGGGCGTGCTCGTGAACAGCCCCAAGGGCATGA	
	AGATCAGCCAGAACTTCGAGACACGCTACCTGATCCTGA	
	GCCTGATCCCCAAGATCGAGGACAGCAACAGCTGCGGC	
	GACCAGCAGATCAAGCAGTACAAGCGGCTGCTGGACAG	
	ACTGATCATCCCCCTGTACGACGGCCTGCGGCTGCAGAA	
	AGACGTGATCGTGACCAACCAGGAAAGCAACGAGAACA	
	CCGACCCCCGGACCGAGAGATTCTTCGGCGGCGTGATCG	
	GCACAATCGCCCTGGGAGTGGCCACAAGCGCCCAGATT	
	ACAGCCGCTGTGGCCCTGGTGGAAGCCAAGCAGGCCAG	
	AAGCGACATCGAGAAGCTGAAAGAGGCCATCCGGGACA	
	CCAACAAGGCCGTGCAGAGCGTGCAGTCCAGCGTGGGC	
	AATCTGATCGTGGCCATCAAGTCCGTGCAGGACTACGTG	
	AACAAAGAAATCGTGCCCTCTATCGCCCGGCTGGGCTGT	
	GAAGCTGCCGGACTGCAGCTGGGCATTGCCCTGACACA	
	GCACTACAGCGAGCTGACCAACATCTTCGGCGACAACA	
	TCGGCAGCCTGCAGGAAAAGGGCATTAAGCTGCAGGGA	
	ATCGCCAGCCTGTACCGCACCAACATCACCGAGATCTTC	
	ACCACCAGCACCGTGGATAAGTACGACATCTACGACCT	
	GCTGTTCACCGAGAGCATCAAAGTGCGCGTGATCGACGT	
	GGACCTGAACGACTACAGCATCACCCTGCAAGTGCGGC	
	TGCCCCTGCTGACCAGACTGCTGAACACCCAGATCTACA	
	AGGTGGACAGCATCTCCTACAACATCCAGAACCGCGAG	
	TGGTACATCCCTCTGCCCAGCCACATTATGACCAAGGGC	
	GCCTTTCTGGGCGGAGCCGACGTGAAAGAGTGCATCGA	
	GGCCTTCAGCAGCTACATCTGCCCCAGCGACCCTGGCTT	
	CGTGCTGAACCACGAGATGGAAAGCTGCCTGAGCGGCA	
	ACATCAGCCAGTGCCCCAGAACCACCGTGACCTCCGAC	
	ATCGTGCCCAGATACGCCTTCGTGAATGGCGGCGTGGTG	
	GCCAACTGCATCACCACCACCTGTACCTGCAACGGCATC	
	GGCAACCGGATCAACCAGCCTCCCGATCAGGGCGTGAA	
	GATTATCACCCACAAAGAGTGTAACACCATCGGCATCA	
	ACGGCATGCTGTTCAATACCAACAAAGAGGGCACCCTG	
	GCCTTCTACACCCCCGACGATATCACCCTGAACAACTCC	
	GTGGCTCTGGACCCCATCGACATCTCCATCGAGCTGAAC	
	AAGGCCAAGAGCGACCTGGAAGAGTCCAAAGAGTGGAT	

TABLE 5 -continued

Description	Sequence	SEQ ID NO:
	CCGGCGGAGCAACCAGAAGCTGGACTCTATCGGCAGCT GGCACCAGAGCAGCACCACCATCATCGTGATCCTGATTA TGATGATTATCCTGTTCATCATCAACATTACCATCATCAC TATCGCCATTAAGTACTACCGGATCCAGAAACGGAACC GGGTGGACCAGAATGACAAGCCCTACGTGCTGACAAAC AAG	
	PIV3 mRNA Sequences	
>gb|KJ672601.1|: 4990-6609 Human parainfluenza virus 3 strain HPIV3/*Homo sapiens*/ PER/FLA4815/ 2008 [fusion glycoprotein F0]	AUGCCAAUUUCAAUACUGUUAAUUAUUACAACCAUGA UCAUGGCAUCACACUGCCAAAUAGACAUCACAAAACU ACAGCAUGUAGGUGUAUUGGUCAACAGUCCCAAAGGG AUGAAGAUAUCACAAAACUUCGAAACAAGAUAUCUAA UCCUGAGUCUCAUACCAAAAAUAGAAGAUUCUAACUC UUGUGGUGACCAACAGAUCAAGCAAUACAAGAGGUUA UUGGAUAGACUGAUCAUUCCUUUAUAUGAUGGACUAA GAUUACAGAAGGAUGUGAUAGUGACUAAUCAAGAAUC CAAUGAAAACACUGAUCCCAGAACAGAACGAUUCUUU GGAGGGGUAAUUGGAACUAUUGCUCUAGGAGUAGCAA CCUCAGCACAAAUUACAGCAGCAGUUGCUCUGGUUGA AGCCAAGCAGGCAAGAUCAGACAUUGAAAAACUCAAG GAAGCAAUCAGGGACACAAAUAAAGCAGUGCAGUCAG UUCAGAGCUCUGUAGGAAAUUUGAUAGUAGCAAUUAA AUCAGUCCAGGAUUAUGUCAACAAAGAAAUCGUGCCA UCGAUUGCGAGACUAGGUUGUGAAGCAGCAGGACUUC AGUUAGGGAUUGCAUUAACACAGCAUUACUCAGAAUU AACAAAUAUAUUUGGUGAUAACAUAGGAUCGUUACAA GAAAAAGGAAUAAAAUUACAAGGUAUAGCAUCAUUAU ACCGUACAAAUAUCACAGAAAUAUUCACAACAUCAAC AGUUGACAAAUAUGAUAUUUAUGAUCUAUUAUUUACA GAAUCAAUAAAGGUGAGAGUUAUAGAUGUUGAUUUGA AUGAUUACUCAAUAACCCUCCAAGUCAGACUCCCUUU AUUGACCAGACUGCUGAACACUCAAAUCUACAAAGUA GAUUCCAUAUCAUACAAUAUCCAAAAUAGAGAAUGGU AUAUCCCUCUUCCCAGCCAUAUCAUGACGAAAGGGGC AUUUCUAGGUGGAGCAGAUGUCAAAGAAUGCAUAGAA GCAUUCAGCAGUUAUAUAUGCCCUUCUGAUCCAGGAU UUGUACUAAACCAUGAAAUGGAGAGCUGUCUAUCAGG AAACAUAUCCCAAUGUCCAAGAACCACAGUCACAUCA GACAUAGUUCCUAGGUAUGCAUUUGUCAAUGGAGGAG UGGUUGCGAAUUGUAUAACAACUACAUGUACAUGCAA UGGUAUCGGUAAUAGAAUCAACCAACCACCUGAUCAA GGAGUCAAAAUUAUAACACAUAAAGAAUGUAAUACAA UAGGUAUCAACGGAAUGCUAUUCAACACAAACAAAGA AGGAACUCUUGCAUUCUACACACCAGACGACAUAACA UUAAACAAUUCUGUUGCACUUGAUCCGAUUGACAUAU CAAUCGAGCUCAACAAGGCCAAAUCAGAUCUUGAGGA AUCAAAAGAAUGGAUAAGAAGGUCAAAUCAAAAGCUA GAUUCUAUUGGAAGUUGGCAUCAAUCUAGCACUACAA UCAUAGUUAUUUUGAUAAUGAUGAUUAUAUUGUUUAU AAUUAAUAUAACAAUAAUUACAAUUGCAAUUAAGUAU UACAGAAUUCAAAAGAGAAAUCGAGUGGAUCAAAAUG AUAAGCCGUAUGUAUUAACAAACAAG	61
gi|612507167|gb| AHX22430.1| hemagglutinin-neuraminidase [Human parainfluenza virus 3]	AUGGAAUACUGGAAGCACACCAACCACGGAAAGGAUG CUGGUAAUGAGCUGGAGACAUCCACAGCCACUCAUGG CAACAAGCUCACCAACAAGAUAACAUAUAUAUUGUGG ACGAUAACCCUGGUGUUAUUAUCAAUAGUCUUCAUCA UAGUGCUAACUAAUUCCAUCAAAAGUGAAAAGGCCCG CGAAUCAUUGCUACAAGACAUAAAUAAUGAGUUUAUG GAAGUUACAGAAAAGAUCCAAGUGGCAUCGGAUAAUA CUAAUGAUCUAAUACAGUCAGGAGUGAAUACAAGGCU UCUUACAAUUCAGAGUCAUGUCCAGAAUUAUAUACCA AUAUCAUUGACACAACAAAUAUCGGAUCUUAGGAAAU UCAUUAGUGAAAUUACAAUUAGAAAUGAUAAUCAAGA AGUGCCACCACAAAGAAUAACACAUGAUGUGGGUAUA AAACCUUUAAAUCCAGAUGAUUUCUGGAGAUGCACGU CUGGUCUUCCAUCUUUGAUGAAAACUCCAAAAAUAAG AUUAAUGCCGGGACCAGGAUUAUUAGCUAUGCCAACG ACUGUUGAUGGCUGUGUCAGAACCCCGUCCUUAGUGA UAAAUGAUCUGAUUUAUGCUUACACCUCAAAUCUAAU UACUCGAGGUUGCCAGGAUAUAGGGAAAUCAUAUCAA GUAUUACAGAUAGGGAUAAUAACUGUAAACUCAGACU UGGUACCUGACUUAAAUCCUAGGAUCUCUCAUACCUU CAACAUAAAUGACAAUAGAAAGUCAUGUUCUCUAGCA CUCCUAAAUACAGAUGUAUAUCAACUGUGUUCAACCC	62

TABLE 5 -continued

Description	Sequence	SEQ ID NO:
	CAAAAGUUGAUGAAAGAUCAGAUUAUGCAUCAUCAGG	
	CAUAGAAGAUAUUGUACUUGAUAUUGUCAAUUAUGAU	
	GGCUCAAUCUCGACAACAAGAUUUAAGAAUAAUAAUA	
	UAAGUUUUGAUCAACCAUAUGCGGCAUUAUACCCAUC	
	UGUUGGACCAGGGAUAUACUACAAAGGCAAAAUAAUA	
	UUUCUCGGGUAUGGAGGUCUUGAACAUCCAAUAAAUG	
	AGAAUGCAAUCUGCAACACAACUGGGUGUCCUGGGAA	
	AACACAGAGAGACUGUAAUCAAGCAUCUCAUAGUCCA	
	UGGUUUUCAGAUAGAAGGAUGGUCAACUCUAUAAUUG	
	UUGUUGACAAGGGCUUGAACUCAGUUCCAAAAUUGAA	
	GGUAUGGACGAUAUCUAUGAGACAAAAUUACUGGGGG	
	UCAGAAGGAAGAUUACUUCUACUAGGUAACAAGAUCU	
	ACAUAUACACAAGAUCUACAAGUUGGCACAGCAAGUU	
	ACAAUUAGGAAUAAUUGACAUUACUGACUACAGUGAU	
	AUAAGGAUAAAAUGGACAUGGCAUAAUGUGCUAUCAA	
	GACCAGGAAACAAUGAAUGUCCAUGGGGACAUUCAUG	
	UCCGGAUGGAUGUAUAACGGGAGUAUAUACCGAUGCA	
	UAUCCACUCAAUCCCACAGGAAGCAUUGUAUCAUCUG	
	UCAUAUUGGACUCACAAAAAUCGAGAGUCAACCCAGU	
	CAUAACUUACUCAACAGCAACCGAAAGGGUAAACGAG	
	CUGGCUAUCCGAAACAAAACACUCUCAGCUGGGUACA	
	CAACAACAAGCUGCAUUACACACUAUAACAAAGGGUA	
	UUGUUUUCAUAUAGUAGAAAUAAAUCAUAAAAGCUUA	
	AACACAUUUCAACCCAUGUUGUUCAAAACAGAGAUUC	
	CAAAAAGCUGCAGU	
HPIV3_HN_Codon Optimized	AUGGAAUACUGGAAGCACACCAACCACGGCAAGGACG	63
	CCGGCAACGAGCUGGAAACCAGCACAGCCACACACGGC	
	AACAAGCUGACCAACAAGAUCACCUACAUCCUGUGGA	
	CCAUCACCCUGGUGCUGCUGAGCAUCGUGUUCAUCAUC	
	GUGCUGACCAAUAGCAUCAAGAGCGAGAAGGCCAGAG	
	AGAGCCUGCUGCAGGACAUCAACAACGAGUUCAUGGA	
	AGUGACCGAGAAGAUCCAGGUGGCCAGCGACAACACC	
	AACGACCUGAUCCAGAGCGGCGUGAACACCCGGCUGCU	
	GACCAUCCAGAGCCACGUGCAGAACUACAUCCCCAUCA	
	GCCUGACCCAGCAGAUCAGCGACCUGCGGAAGUUCAUC	
	AGCGAGAUCACCAUCCGGAACGACAACCAGGAAGUGC	
	CCCCCCAGAGAAUCACCCACGACGUGGGCAUCAAGCCC	
	CUGAACCCCGACGAUUUCUGGCGGUGUACAAGCGGCC	
	UGCCCAGCCUGAUGAAGACCCCCAAGAUCCGGCUGAUG	
	CCUGGCCCUGGACUGCUGGCCAUGCCUACCACAGUGGA	
	UGGCUGUGUGCGGACCCCCAGCCUCGUGAUCAACGAUC	
	UGAUCUACGCCUACACCAGCAACCUGAUCACCCGGGGC	
	UGCCAGGAUAUCGGCAAGAGCUACCAGGUGCUGCAGA	
	UCGGCAUCAUCACCGUGAACUCCGACCUGGUGCCCGAC	
	CUGAACCCUCGGAUCAGCCACACCUUCAACAUCAACGA	
	CAACAGAAAGAGCUGCAGCCUGGCUCUGCUGAACACC	
	GACGUGUACCAGCUGUGCAGCACCCCCAAGGUGGACG	
	AGAGAAGCGACUACGCCAGCAGCGGCAUCGAGGAUAU	
	CGUGCUGGACAUCGUGAACUACGACGGCAGCAUCAGC	
	ACCACCCGGUUCAAGAACAACAACAUCAGCUUCGACCA	
	GCCCUACGCCGCCCUGUACCCUUCUGUGGGCCCUGGCA	
	UCUACUACAAGGGCAAGAUCAUCUUCCUGGGCUACGG	
	CGGCCUGGAACACCCCAUCAACGAGAACGCCAUCUGCA	
	ACACCACCGGCUGCCCUGGCAAGACCCAGAGAGACUGC	
	AAUCAGGCCAGCCACAGCCCCUGGUUCAGCGACCGCAG	
	AAUGGUCAACUCUAUCAUCGUGGUGGACAAGGGCCUG	
	AACAGCGUGCCCAAGCUGAAAGUGUGGACAAUCAGCA	
	UGCGCCAGAACUACUGGGGCAGCGAGGGCAGACUUCU	
	GCUGCUGGGAAACAAGAUCUACAUCUACACCCGGUCC	
	ACCAGCUGGCACAGCAAACUGCAGCUGGGAAUCAUCG	
	ACAUCACCGACUACAGCGACAUCCGGAUCAAGUGGACC	
	UGGCACAACGUGCUGAGCAGACCCGGCAACAAUGAGU	
	GCCCUUGGGGCCACAGCUGCCCCGAUGGAUGUAUCACC	
	GGCGUGUACACCGACGCCUACCCCCUGAAUCCUACCGG	
	CUCCAUCGUGUCCAGCGUGAUCCUGGACAGCCAGAAA	
	AGCAGAGUGAACCCCGUGAUCACAUACAGCACCGCCAC	
	CGAGAGAGUGAACGAACUGGCCAUCAGAAACAAGACC	
	CUGAGCGCCGGCUACACCACCACAAGCUGCAUCACACA	
	CUACAACAAGGGCUACUGCUUCCACAUCGUGGAAAUC	
	AACCACAAGUCCCUGAACACCUUCCAGCCCAUGCUGUU	
	CAAGACCGAGAUCCCCAAGAGCUGCUCC	
HPIV3_F_Codon Optimized mRNA sequence	AUGCCCAUCAGCAUCCUGCUGAUCAUCACCACAAUGAU	64
	CAUGGCCAGCCACUGCCAGAUCGACAUCACCAAGCUGC	
	AGCACGUGGGCGUGCUCGUGAACAGCCCCAAGGGCAU	

TABLE 5 -continued

Description	Sequence	SEQ ID NO:
	GAAGAUCAGCCAGAACUUCGAGACACGCUACCUGAUC	
	CUGAGCCUGAUCCCCAAGAUCGAGGACAGCAACAGCU	
	GCGGCGACCAGCAGAUCAAGCAGUACAAGCGGCUGCU	
	GGACAGACUGAUCAUCCCCCUGUACGACGGCCUGCGGC	
	UGCAGAAAGACGUGAUCGUGACCAACCAGGAAAGCAA	
	CGAGAACACCGACCCCCGGACCGAGAGAUUCUUCGGCG	
	GCGUGAUCGGCACAAUCGCCCUGGGAGUGGCCACAAG	
	CGCCCAGAUUACAGCCGCUGUGGCCCUGGUGGAAGCCA	
	AGCAGGCCAGAAGCGACAUCGAGAAGCUGAAAGAGGC	
	CAUCCGGGACACCAACAAGGCCGUGCAGAGCGUGCAG	
	UCCAGCGUGGGCAAUCUGAUCGUGGCCAUCAAGUCCG	
	UGCAGGACUACGUGAACAAAGAAAUCGUGCCCUCUAU	
	CGCCCGGCUGGGCUGUGAAGCUGCCGGACUGCAGCUG	
	GGCAUUGCCCUGACACAGCACUACAGCGAGCUGACCAA	
	CAUCUUCGGCGACAACAUCGGCAGCCUGCAGGAAAAG	
	GGCAUUAAGCUGCAGGGAAUCGCCAGCCUGUACCGCA	
	CCAACAUCACCGAGAUCUUCACCACCAGCACCGUGGAU	
	AAGUACGACAUCUACGACCUGCUGUUCACCGAGAGCA	
	UCAAAGUGCGCGUGAUCGACGUGGACCUGAACGACUA	
	CAGCAUCACCCUGCAAGUGCGGCUGCCCCUGCUGACCA	
	GACUGCUGAACACCCAGAUCUACAAGGUGGACAGCAU	
	CUCCUACAACAUCCAGAACCGCGAGUGGUACAUCCCUC	
	UGCCCAGCCACAUUAUGACCAAGGGCGCCUUUCUGGGC	
	GGAGCCGACGUGAAAGAGUGCAUCGAGGCCUUCAGCA	
	GCUACAUCUGCCCCAGCGACCCUGGCUUCGUGCUGAAC	
	CACGAGAUGGAAAGCUGCCUGAGCGGCAACAUCAGCC	
	AGUGCCCCAGAACCACCGUGACCUCCGACAUCGUGCCC	
	AGAUACGCCUUCGUGAAUGGCGGCGUGGUGGCCAACU	
	GCAUCACCACCACCUGUACCUGCAACGGCAUCGGCAAC	
	CGGAUCAACCAGCCUCCCGAUCAGGGCGUGAAGAUUA	
	UCACCCACAAAGAGUGUAACACCAUCGGCAUCAACGGC	
	AUGCUGUUCAAUACCAACAAAGAGGGCACCCUGGCCU	
	UCUACACCCCCGACGAUAUCACCCUGAACAACUCCGUG	
	GCUCUGGACCCCAUCGACAUCUCCAUCGAGCUGAACAA	
	GGCCAAGAGCGACCUGGAAGAGUCCAAAGAGUGGAUC	
	CGGCGGAGCAACCAGAAGCUGGACUCUAUCGGCAGCU	
	GGCACCAGAGCAGCACCACCAUCAUCGUGAUCCUGAUU	
	AUGAUGAUUAUCCUGUUCAUCAUCAACAUUACCAUCA	
	UCACUAUCGCCAUUAAGUACUACCGGAUCCAGAAACG	
	GAACCGGGUGGACCAGAAUGACAAGCCCUACGUGCUG	
	ACAAACAAG	

TABLE 6

PIV3 Amino Acid Sequences

Description	Sequence	SEQ ID NO:
>gi|612507166|gb|AHX22429.1| fusion glycoprotein F0 [Human parainfluenza virus 3]	MPISILLIITTMIMASHCQIDITKLQHVGVLVNSPKGMKISQ NFETRYLILSLIPKIEDSNSCGDQQIKQYKRLLDRLIIPLYDG LRLQKDVIVTNQESNENTDPRTERFFGGVIGTIALGVATSA QITAAVALVEAKQARSDIEKLKEAIRDTNKAVQSVQSSVG NLIVAIKSVQDYVNKEIVPSIARLGCEAAGLQLGIALTQHYS ELTNIFGDNIGSLQEKGIKLQGIASLYRTNITEIFTTSTVDKY DIYDLLFTESIKVRVIDVDLNDYSITLQVRLPLLTRLLNTQIY KVDSISYNIQNREWYIPLPSHIMTKGAFLGGADVKECIEAFS SYICPSDPGFVLNHEMESCLSGNISQCPRTTVTSDIVPRYAF VNGGVVANCITTTCTCNGIGNRINQPPDQGVKIITHKECNTI GINGMLFNTNKEGTLAFYTPDDITLNNSVALDPIDISIELNK AKSDLEESKEWIRRSNQKLDSIGSWHQSSTTIIVILIMMIILFI INITIITIAIKYYRIQKRNRVDQNDKPYVLTNK	13
gi|612507167|gb|AHX22430.1| hemagglutinin-neuraminidase [Human parainfluenza virus 3]	MEYWKHTNHGKDAGNELETSTATHGNKLTNKITYILWTIT LVLLSIVFIIVLTNSIKSEKARESLLQDINNEFMEVTEKIQVA SDNTNDLIQSGVNTRLLTIQSHVQNYIPISLTQQISDLRKFIS EITIRNDNQEVPPQRITHDVGIKPLNPDDFWRCTSGLPSLMK TPKIRLMPGPGLLAMPTTVDGCVRTPSLVINDLIYAYTSNLI TRGCQDIGKSYQVLQIGIITVNSDLVPDLNPRISHTFNINDN RKSCSLALLNTDVYQLCSTPKVDERSDYASSGIEDIVLDIV NYDGSISTTRFKNNNISFDQPYAALYPSVGPGIYYKGKIIFL GYGGLEHPINENAICNTTGCPGKTQRDCNQASHSPWFSDR	14

TABLE 6-continued

PIV3 Amino Acid Sequences

Description	Sequence	SEQ ID NO:
	RMVNSIIVVDKGLNSVPKLKVWTISMRQNYWGSEGRLLLL GNKIYIYTRSTSWHSKLQLGIIDITDYSDIRIKWTWHNVLSR PGNNECPWGHSCPDGCITGVYTDAYPLNPTGSIVSSVILDS QKSRVNPVITYSTATERVNELAIRNKTLSAGYTTTSCITHY NKGYCFHIVEINHKSLNTFQPMLFKTEIPKSCS	

TABLE 7

PIV3 NCBI Accession Numbers (Nucleic Acid and Amino Acid Sequences)

Description	GenBank Accession
Fusion glycoprotein F0 [Human parainfluenza virus 3] HPIV3/*Homo sapiens*/PER/FLA4815/2008	KJ672601.1|: 4990-6609 AHX22429 (Fusion protein)
hemagglutinin-neuraminidase [Human parainfluenza virus 3] HPIV3/*Homo sapiens*/PER/FLA4815/2008	KJ672601.1|: 6724-8442 AHX22430 (HN protein)
Recombinant PIV3/PIV1 virus fusion glycoprotein (F) and hemagglutinin (HN) genes, complete cds; and RNA dependent RNA polymerase (L) gene, partial cds.	AF016281 AAC23947 (hemagglutinin)
Recombinant PIV3/PIV1 virus fusion glycoprotein (F) and hemagglutinin (HN) genes, complete cds; and RNA dependent RNA polymerase (L) gene, partial cds.	AF016281 AAC23947 (fusion protein)
hemagglutinin-neuraminidase [Human parainfluenza virus 3]	BAO32044.1
hemagglutinin-neuraminidase [Human parainfluenza virus 3]	BAO32051.1
C protein [Human parainfluenza virus 3]	NP_599251.1
C protein [Human parainfluenza virus 3]	ABZ85670.1
C protein [Human parainfluenza virus 3]	AGT75164.1
C protein [Human parainfluenza virus 3]	AAB48686.1
C protein [Human parainfluenza virus 3]	AHX22115.1
C protein [Human parainfluenza virus 3]	AGW51066.1
C protein [Human parainfluenza virus 3]	AGW51162.1
C protein [Human parainfluenza virus 3]	AGT75252.1
C protein [Human parainfluenza virus 3]	AGT75188.1
C protein [Human parainfluenza virus 3]	AGW51218.1
C protein [Human parainfluenza virus 3]	AGW51074.1
C protein [Human parainfluenza virus 3]	AGT75323.1
C protein [Human parainfluenza virus 3]	AGT75307.1
C protein [Human parainfluenza virus 3]	AHX22131.1
C protein [Human parainfluenza virus 3]	AGW51243.1
C protein [Human parainfluenza virus 3]	AGT75180.1
C protein [Human parainfluenza virus 3]	AGT75212.1
C protein [Human parainfluenza virus 3]	AGW51186.1
C protein [Human parainfluenza virus 3]	AHX22075.1
C protein [Human parainfluenza virus 3]	AHX22163.1
C protein [Human parainfluenza virus 3]	AGT75196.1
C protein [Human parainfluenza virus 3]	AHX22491.1
C protein [Human parainfluenza virus 3]	AHX22139.1
C protein [Human parainfluenza virus 3]	AGW51138.1
C protein [Human parainfluenza virus 3]	AGW51114.1
C protein [Human parainfluenza virus 3]	AGT75220.1
C protein [Human parainfluenza virus 3]	AHX22251.1
RecName: Full = Protein C; AltName: Full = VP18 protein	P06165.1
C protein [Human parainfluenza virus 3]	AHX22187.1
C protein [Human parainfluenza virus 3]	AGT75228.1
C protein [Human parainfluenza virus 3]	AHX22179.1
C protein [Human parainfluenza virus 3]	AHX22427.1
C protein [Human parainfluenza virus 3]	AGW51210.1
nonstructural protein C [Human parainfluenza virus 3]	BAA00922.1
C protein [Human parainfluenza virus 3]	AHX22315.1
C protein [Human parainfluenza virus 3]	AGW51259.1
C protein [Human parainfluenza virus 3]	AHX22435.1
C protein [Human parainfluenza virus 3]	AHX22123.1
C protein [Human parainfluenza virus 3]	AHX22299.1
C protein [Human parainfluenza virus 3]	AGW51267.1
unnamed protein product [Human parainfluenza virus 3]	CAA28430.1
C protein [Human parainfluenza virus 3]	AGW51178.1
C protein [Human parainfluenza virus 3]	AHX22411.1
RecName: Full = Protein C	P06164.1

TABLE 7-continued

PIV3 NCBI Accession Numbers (Nucleic Acid and Amino Acid Sequences)

Description	GenBank Accession
phosphoprotein [Human parainfluenza virus 3]	NP_067149.1
phosphoprotein [Human parainfluenza virus 3]	AAB48685.1
phosphoprotein [Human parainfluenza virus 3]	AHX22498.1
phosphoprotein [Human parainfluenza virus 3]	AHX22490.1
phosphoprotein [Human parainfluenza virus 3]	AGT75259.1
phosphoprotein [Human parainfluenza virus 3]	AGW51137.1
phosphoprotein [Human parainfluenza virus 3]	AGW51145.1
phosphoprotein [Human parainfluenza virus 3]	AGT75298.1
phosphoprotein [Human parainfluenza virus 3]	AGW51113.1
phosphoprotein [Human parainfluenza virus 3]	AGT75203.1
phosphoprotein [Human parainfluenza virus 3]	AGT75163.1
phosphoprotein [Human parainfluenza virus 3]	AHX22506.1
phosphoprotein [Human parainfluenza virus 3]	AGW51129.1
phosphoprotein [Human parainfluenza virus 3]	AHX22194.1
phosphoprotein [Human parainfluenza virus 3]	AGT75211.1
phosphoprotein [Human parainfluenza virus 3]	AHX22258.1
phosphoprotein [Human parainfluenza virus 3]	AGW51121.1
phosphoprotein [Human parainfluenza virus 3]	AGT75282.1
phosphoprotein [Human parainfluenza virus 3]	AHX22146.1
phosphoprotein [Human parainfluenza virus 3]	AHX22138.1
phosphoprotein [Human parainfluenza virus 3]	AHX22322.1
phosphoprotein [Human parainfluenza virus 3]	AHX22370.1
phosphoprotein [Human parainfluenza virus 3]	AHX22098.1
phosphoprotein [Human parainfluenza virus 3]	AHX22130.1
phosphoprotein [Human parainfluenza virus 3]	AHX22418.1
phosphoprotein [Human parainfluenza virus 3]	AHX22114.1
phosphoprotein [Human parainfluenza virus 3]	AHX22410.1
phosphoprotein [Human parainfluenza virus 3]	AGT75306.1
phosphoprotein [Human parainfluenza virus 3]	AHX22170.1
phosphoprotein [Human parainfluenza virus 3]	AHX22266.1
phosphoprotein [Human parainfluenza virus 3]	AHX22090.1
phosphoprotein [Human parainfluenza virus 3]	AGT75195.1
phosphoprotein [Human parainfluenza virus 3]	AHX22226.1
phosphoprotein [Human parainfluenza virus 3]	AHX22178.1
phosphoprotein [Human parainfluenza virus 3]	AHX22122.1
phosphoprotein [Human parainfluenza virus 3]	AHX22186.1
phosphoprotein [Human parainfluenza virus 3]	AHX22066.1
phosphoprotein [Human parainfluenza virus 3]	AHX22522.1
phosphoprotein [Human parainfluenza virus 3]	AGW51225.1
phosphoprotein [Human parainfluenza virus 3]	BAN29032.1
phosphoprotein [Human parainfluenza virus 3]	ABZ85669.1
phosphoprotein [Human parainfluenza virus 3]	AHX22426.1
phosphoprotein [Human parainfluenza virus 3]	AHX22058.1
phosphoprotein [Simian Agent 10]	ADR00400.1
phosphoprotein [Human parainfluenza virus 3]	AHX22250.1
phosphoprotein [Human parainfluenza virus 3]	AHX22434.1
phosphoprotein [Human parainfluenza virus 3]	AHX22298.1
phosphoprotein [Human parainfluenza virus 3]	AHX22442.1
phosphoprotein [Human parainfluenza virus 3]	AHX22074.1
phosphoprotein [Human parainfluenza virus 3]	AGW51153.1
phosphoprotein [Human parainfluenza virus 3]	AGW51241.1
phosphoprotein [Human parainfluenza virus 3]	AHX22210.1
phosphoprotein [Human parainfluenza virus 3]	AGW51105.1
phosphoprotein [Human parainfluenza virus 3]	AGT75251.1
phosphoprotein [Human parainfluenza virus 3]	AHX22362.1
phosphoprotein [Human parainfluenza virus 3]	AHX22474.1
phosphoprotein [Human parainfluenza virus 3]	AGW51217.1
phosphoprotein [Human parainfluenza virus 3]	AIG60038.1
phosphoprotein [Human parainfluenza virus 3]	AHX22378.1
phosphoprotein [Human parainfluenza virus 3]	AGW51057.1
phosphoprotein [Human parainfluenza virus 3]	AGT75187.1
phosphoprotein [Human parainfluenza virus 3]	AGW51233.1
phosphoprotein [Human parainfluenza virus 3]	AHX22482.1
phosphoprotein [Human parainfluenza virus 3]	AGW51161.1
phosphoprotein [Human parainfluenza virus 3]	AHX22306.1
phosphoprotein [Human parainfluenza virus 3]	AHX22162.1
phosphoprotein [Human parainfluenza virus 3]	ACJ70087.1
phosphoprotein [Human parainfluenza virus 3]	AHX22466.1
phosphoprotein [Human parainfluenza virus 3]	AHX22346.1
phosphoprotein [Human parainfluenza virus 3]	AGW51089.1
phosphoprotein [Human parainfluenza virus 3]	AGW51073.1
phosphoprotein [Human parainfluenza virus 3]	AGW51185.1
phosphoprotein [Human parainfluenza virus 3]	AGW51065.1
phosphoprotein [Human parainfluenza virus 3]	ABY47603.1
phosphoprotein [Human parainfluenza virus 3]	AGW51049.1
phosphoprotein [Human parainfluenza virus 3]	AHX22330.1

TABLE 7-continued

PIV3 NCBI Accession Numbers (Nucleic Acid and Amino Acid Sequences)

Description	GenBank Accession
phosphoprotein [Human parainfluenza virus 3]	AGW51250.1
phosphoprotein [Human parainfluenza virus 3]	AGT75227.1
phosphoprotein [Human parainfluenza virus 3]	AGW51282.1
phosphoprotein [Human parainfluenza virus 3]	AGW51209.1
phosphoprotein [Human parainfluenza virus 3]	AGW51193.1
phosphoprotein [Human parainfluenza virus 3]	AGT75322.1
phosphoprotein [Human parainfluenza virus 3]	AGT75219.1
phosphoprotein [Human parainfluenza virus 3]	AGW51258.1
phosphoprotein [Human parainfluenza virus 3]	AGW51041.1
phosphoprotein [Human parainfluenza virus 3]	ACD99698.1
phosphoprotein [Human parainfluenza virus 3]	AGW51266.1
phosphoprotein [Human parainfluenza virus 3]	AGT75179.1
phosphoprotein [Human parainfluenza virus 3]	AHX22282.1
phosphoprotein [Human parainfluenza virus 3]	AGW51169.1
phosphoprotein [Human parainfluenza virus 3]	AGW51274.1
phosphoprotein [Human parainfluenza virus 3]	AGW51201.1
phosphoprotein [Human parainfluenza virus 3]	AGW51177.1
RecName: Full = Phosphoprotein; Short = Protein P	P06162.1
P protein [Human parainfluenza virus 3]	AAA66818.1
phosphoprotein [Human parainfluenza virus 3]	AAA46866.1
phosphoprotein [Human parainfluenza virus 3]	BAA00031.1
polymerase-associated nucleocapsid phosphoprotein (version 2) - parainfluenza virus type 3 [Human parainfluenza virus 3]	RRNZP5
phosphoprotein [Human parainfluenza virus 3]	AGT75171.1
phosphoprotein [Human parainfluenza virus 3]	BAA00921.1
D protein [Human parainfluenza virus 3]	NP__599250.1
D protein [Human parainfluenza virus 3]	AHX22377.1
D protein [Human parainfluenza virus 3]	AHX22121.1
D protein [Human parainfluenza virus 3]	AGT75297.1
D protein [Human parainfluenza virus 3]	AGW51136.1
D protein [Human parainfluenza virus 3]	AGW51242.1
D protein [Human parainfluenza virus 3]	AGW51112.1
D protein [Human parainfluenza virus 3]	AHX22497.1
D protein [Human parainfluenza virus 3]	AHX22145.1
D protein [Human parainfluenza virus 3]	AGT75202.1
D protein [Human parainfluenza virus 3]	AHX22385.1
D protein [Human parainfluenza virus 3]	AGW51216.1
D protein [Human parainfluenza virus 3]	AGT75281.1
D protein [Human parainfluenza virus 3]	AGT75194.1
D protein [Human parainfluenza virus 3]	AHX22521.1
D protein [Human parainfluenza virus 3]	AGW51120.1
D protein [Human parainfluenza virus 3]	AGT75313.1
D protein [Human parainfluenza virus 3]	AHX22249.1
D protein [Human parainfluenza virus 3]	AHX22097.1
D protein [Human parainfluenza virus 3]	AGW51144.1
D protein [Human parainfluenza virus 3]	AHX22089.1
D protein [Human parainfluenza virus 3]	AHX22225.1
D protein [Human parainfluenza virus 3]	AHX22137.1
D protein [Human parainfluenza virus 3]	AHX22065.1
D protein [Human parainfluenza virus 3]	AGW51224.1
D protein [Human parainfluenza virus 3]	AGT75210.1
D protein [Human parainfluenza virus 3]	AHX22393.1
D protein [Human parainfluenza virus 3]	AGT75258.1
D protein [Human parainfluenza virus 3]	AHX22345.1
D protein [Human parainfluenza virus 3]	AGT75250.1
D protein [Human parainfluenza virus 3]	AHX22113.1
D protein [Human parainfluenza virus 3]	AGW51232.1
D protein [Human parainfluenza virus 3]	AHX22057.1
D protein [Human parainfluenza virus 3]	AHX22209.1
D protein [Human parainfluenza virus 3]	AGW51056.1
D protein [Human parainfluenza virus 3]	AHX22161.1
D protein [Simian Agent 10]	ADR00402.1
D protein [Human parainfluenza virus 3]	AHX22361.1
D protein [Human parainfluenza virus 3]	AGW51281.1
D protein [Human parainfluenza virus 3]	AGW51184.1
D protein [Human parainfluenza virus 3]	AGW51160.1
D protein [Human parainfluenza virus 3]	AHX22465.1
D protein [Human parainfluenza virus 3]	AHX22329.1
D protein [Human parainfluenza virus 3]	AGW51064.1
D protein [Human parainfluenza virus 3]	AGW51040.1
D protein [Human parainfluenza virus 3]	AGT75226.1
D protein [Human parainfluenza virus 3]	AHX22425.1
D protein [Human parainfluenza virus 3]	AHX22305.1
D protein [Human parainfluenza virus 3]	AGW51249.1
D protein [Human parainfluenza virus 3]	AHX22481.1

TABLE 7-continued

PIV3 NCBI Accession Numbers (Nucleic Acid and Amino Acid Sequences)

Description	GenBank Accession
D protein [Human parainfluenza virus 3]	AHX22281.1
D protein [Human parainfluenza virus 3]	AGW51048.1
D protein [Human parainfluenza virus 3]	AHX22297.1
D protein [Human parainfluenza virus 3]	AGW51088.1
D protein [Human parainfluenza virus 3]	AGT75305.1
D protein [Human parainfluenza virus 3]	AHX22185.1
D protein [Human parainfluenza virus 3]	AGW51104.1
D protein [Human parainfluenza virus 3]	AHX22081.1
D protein [Human parainfluenza virus 3]	AGW51192.1
D protein [Human parainfluenza virus 3]	AHX22489.1
D protein [Human parainfluenza virus 3]	AHX22441.1
D protein [Human parainfluenza virus 3]	AHX22409.1
D protein [Human parainfluenza virus 3]	AHX22369.1
D protein [Human parainfluenza virus 3]	AHX22321.1
D protein [Human parainfluenza virus 3]	AHX22073.1
D protein [Human parainfluenza virus 3]	AGW51152.1
D protein [Human parainfluenza virus 3]	AGW51072.1
D protein [Human parainfluenza virus 3]	AGT75321.1
D protein [Human parainfluenza virus 3]	AHX22257.1
D protein [Human parainfluenza virus 3]	AHX22129.1
D protein [Human parainfluenza virus 3]	AHX22417.1
D protein [Human parainfluenza virus 3]	AGT75218.1
D protein [Human parainfluenza virus 3]	AHX22265.1
D protein [Human parainfluenza virus 3]	AGT75178.1
D protein [Human parainfluenza virus 3]	AHX22433.1
D protein [Human parainfluenza virus 3]	AGW51273.1
D protein [Human parainfluenza virus 3]	AGW51208.1
D protein [Human parainfluenza virus 3]	AGT75170.1
D protein [Human parainfluenza virus 3]	AGT75162.1
D protein [Human parainfluenza virus 3]	AGW51257.1
D protein [Human parainfluenza virus 3]	AGW51200.1
D protein [Human parainfluenza virus 3]	AGW51176.1
D protein [Human parainfluenza virus 3]	AGT75186.1
D protein [Human parainfluenza virus 3]	AGW51265.1
D protein [Human parainfluenza virus 3]	AGW51168.1

TABLE 8

Signal Peptides

Description	Sequence	SEQ ID NO:
HuIgG$_k$ signal peptide	METPAQLLFLLL LWLPDTTG	15
IgE heavy chain epsilon -1 signal peptide	MDWTWILFLVAA ATRVHS	16
Japanese encephalitis PRM signal sequence	MLGSNSGQRVVF TILLLLVAPAYS	17
VSVg protein signal sequence	MKCLLYLAFLFI GVNCA	18
Japanese encephalitis JEV signal sequence	MWLVSLAIVTAC AGA	19

TABLE 9

hMPV/PIV Cotton Rat Challenge Study Design

Group	n	Test Article	[conc]/μg	Route	Challenge
1	5	Placebo	n/a	IM	hMPV/A2
2	5	hMPV vaccine mRNA	30	IM	hMPV/A2
3	5	hMPV vaccine mRNA	15	IM	hMPV/A2
4	5	hMPV vaccine mRNA	10	IM	hMPV/A2
5	5	hMPV/PIV3 vaccine mRNA (15/15)	30	IM	hMPV/A2
6	5	FI-hMPV	n/a	IM	hMPV/A2
7	5	Placebo	n/a	IM	PIV3
8	5	PIV3 vaccine mRNA	30	IM	PIV3
9	5	PIV3 vaccine mRNA	15	IM	PIV3
10	5	PIV3 vaccine mRNA	10	IM	PIV3
11	5	hMPV/PIV3 vaccine mRNA (15/15)	30	IM	PIV3
12	5	FI-PIV3	n/a	IM	PIV3

TABLE 10

Strain	Nucleic Acid Sequence	SEQ ID NO:
Betacoronavirus Nucleic Acid Sequence		
gb|KJ156934.1|: 21405-25466 Middle East respiratory	ATGATACACTCAGTGTTTCTACTGATGTTCTTGTTAACACC TACAGAAAGTTACGTTGATGTAGGGCCAGATTCTGTTAAG TCTGCTTGTATTGAGGTTGATATACAACAGACCTTCTTTGA	20

TABLE 10-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
syndrome coronavirus isolate Riyadh_14_2013, spike protein (nucleotide)	TAAAACTTGGCCTAGGCCAATTGATGTTTCTAAGGCTGAC GGTATTATATACCCTCAAGGCCGTACATATTCTAACATAA CTATCACTTATCAAGGTCTTTTTCCCTATCAGGGAGACCAT GGTGATATGTATGTTTACTCTGCAGGACATGCTACAGGCA CAACTCCACAAAAGTTGTTTGTAGCTAACTATTCTCAGGA CGTCAAACAGTTTGCTAATGGGTTTGTCGTCCGTATAGGA GCAGCTGCCAATTCCACTGGCACTGTTATTATTAGCCCATC TACCAGCGCTACTATACGAAAAATTTACCCTGCTTTTATGC TGGGTTCTTCAGTTGGTAATTTCTCAGATGGTAAAATGGG CCGCTTCTTCAATCATACTCTAGTTCTTTTGCCCGATGGAT GTGGCACTTTACTTAGAGCTTTTTATTGTATTCTAGAGCCT CGCTCTGGAAATCATTGTCCTGCTGGCAATTCCTATACTTC TTTTGCCACTTATCACACTCCTGCAACAGATTGTTCTGATG GCAATTACAATCGTAATGCCAGTCTGAACTCTTTTAAGGA GTATTTTAATTTACGTAACTGCACCTTTATGTACACTTATA ACATTACCGAAGATGAGATTTTAGAGTGGTTTGGCATTAC ACAAACTGCTCAAGGTGTTCACCTCTTCTCATCTCGGTATG TTGATTTGTACGGCGGCAATATGTTTCAATTTGCCACCTTG CCTGTTTATGATACTATTAAGTATTATTCTATCATTCCTCA CAGTATTCGTTCTATCCAAAGTGATAGAAAAGCTTGGGCT GCCTTCTACGTATATAAACTTCAACCGTTAACTTTCCTGTT GGATTTTTCTGTTGATGGTTATATACGCAGAGCTATAGACT GTGGTTTTAATGATTTGTCACAACTCCACTGCTCATATGAA TCCTTCGATGTTGAATCTGGAGTTTATTCAGTTTCGTCTTT CGAAGCAAAACCTTCTGGCTCAGTTGTGGAACAGGCTGAA GGTGTTGAATGTGATTTTTCACCTCTTCTGTCTGGCACACC TCCTCAGGTTTATAATTTCAAGCGTTTGGTTTTTACCAATT GCAATTATAATCTTACCAAATTGCTTTCACTTTTTTCTGTG AATGATTTTACTTGTAGTCAAATATCTCCAGCAGCAATTGC TAGCAACTGTTATTCTTCACTGATTTTGGATTATTTTTCAT ACCCACTTAGTATGAAATCCGATCTCAGTGTTAGTTCTGCT GGTCCAATATCCCAGTTTAATTATAAACAGTCCTTTTCTAA TCCCACATGTTTGATCTTAGCGACTGTTCCTCATAACCTTA CTACTATTACTAAGCCTCTTAAGTACAGCTATATTAACAA GTGCTCTCGTCTTCTTTCTGATGATCGTACTGAAGTACCTC AGTTAGTGAACGCTAATCAATACTCACCCTGTGTATCCATT GTCCCATCCACTGTGTGGGAAGACGGTGATTATTATAGGA AACAACTATCTCCACTTGAAGGTGGTGGCTGGCTTGTTGC TAGTGGCTCAACTGTTGCCATGACTGAGCAATTACAGATG GGCTTTGGTATTACAGTTCAATATGGTACAGACACCAATA GTGTTTGCCCCAAGCTTGAATTTGCTAATGACACAAAAAT TGCCTCTCAATTAGGCAATTGCGTGGAATATTCCCTCTATG GTGTTTCGGGCCGTGGTGTTTTTCAGAATTGCACAGCTGTA GGTGTTCGACAGCAGCGCTTTGTTTATGATGCGTACCAGA ATTTAGTTGGCTATTATTCTGATGATGGCAACTACTACTGT CTGCGTGCTTGTGTTAGTGTTCCTGTTTCTGTCATCTATGA TAAAGAAACTAAAACCCACGCTACTCTATTTGGTAGTGTT GCATGTGAACACATTTCTTCTACCATGTCTCAATACTCCCG TTCTACGCGATCAATGCTTAAACGGCGAGATTCTACATAT GGCCCCCTTCAGACACCTGTTGGTTGTGTCCTAGGACTTGT TAATTCCTCTTTGTTCGTAGAGGACTGCAAGTTGCCTCTCG GTCAATCTCTCTGTGCTCTTCCTGACACACCTAGTACTCTC ACACCTCGCAGTGTGCGCTCTGTGCCAGGTGAAATGCGCT TGGCATCCATTGCTTTTAATCATCCCATTCAGGTTGATCAA CTTAATAGTAGTTATTTTAAATTAAGTATACCCACTAATTT TTCCTTTGGTGTGACTCAGGAGTACATTCAGACAACCATTC AGAAAGTTACTGTTGATTGTAAACAGTACGTTTGCAATGG TTTCCAGAAGTGTGAGCAATTACTGCGCGAGTATGGCCAG TTTTGTTCCAAAATAAACCAGGCTCTCCATGGTGCCAATTT ACGCCAGGATGATTCTGTACGTAATTTGTTTGCGAGCGTG AAAAGCTCTCAATCATCTCCTATCATACCAGGTTTTGGAG GTGACTTTAATTTGACACTTCTAGAACCTGTTTCTATATCT ACTGGCAGTCGTAGTGCACGTAGTGCTATTGAGGATTTGC TATTTGACAAAGTCACTATAGCTGATCCTGGTTATATGCA AGGTTACGATGATTGTATGCAGCAAGGTCCAGCATCAGCT CGTGATCTTATTTGTGCTCAATATGTGGCTGGTTATAAAGT ATTACCTCCTCTTATGGATGTTAATATGGAAGCCGCGTATA CTTCATCTTTGCTTGGCAGCATAGCAGGTGTTGGCTGGACT GCTGGCTTATCCTCCTTTGCTGCTATTCCATTTGCACAGAG TATYTTTTATAGGTTAAACGGTGTTGGCATTACTCAACAG GTTCTTTCAGAGAACCAAAAGCTTATTGCCAATAAGTTTA ATCAGGCTCTGGGAGCTATGCAAACAGGCTTCACTACAAC TAATGAAGCTTTTCGGAAGGTTCAGGATGCTGTGAACAAC AATGCACAGGCTCTATCCAAATTAGCTAGCGAGCTATCTA ATACTTTTGGTGCTATTTCCGCCTCTATTGGAGACATCATA CAACGTCTTGATGTTCTCGAACAGGACGCCCAAATAGACA GACTTATTAATGGCCGTTTGACAACACTAAATGCTTTTGTT	

TABLE 10-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
	GCACAGCAGCTTGTTCGTTCCGAATCAGCTGCTCTTTCCGC	
	TCAATTGGCTAAAGATAAAGTCAATGAGTGTGTCAAGGCA	
	CAATCCAAGCGTTCTGGATTTTGCGGTCAAGGCACACATA	
	TAGTGTCCTTTGTTGTAAATGCCCCTAATGGCCTTTACTTT	
	ATGCATGTTGGTTATTACCCTAGCAACCACATTGAGGTTGT	
	TTCTGCTTATGGTCTTTGCGATGCAGCTAACCCTACTAATT	
	GTATAGCCCCTGTTAATGGCTACTTTATTAAAACTAATAAC	
	ACTAGGATTGTTGATGAGTGGTCATATACTGGCTCGTCCTT	
	CTATGCACCTGAGCCCATCACCTCTCTTAATACTAAGTATG	
	TTGCACCACAGGTGACATACCAAAACATTTCTACTAACCT	
	CCCTCCTCCTCTTCTCGGCAATTCCACCGGGATTGACTTCC	
	AAGATGAGTTGGATGAGTTTTTCAAAAATGTTAGCACCAG	
	TATACCTAATTTTGGTTCTCTAACACAGATTAATACTACAT	
	TACTCGATCTTACCTACGAGATGTTGTCTCTTCAACAAGTT	
	GTTAAAGCCCTTAATGAGTCTTACATAGACCTTAAAGAGC	
	TTGGCAATTATACTTATTACAACAAATGGCCGTGGTACAT	
	TTGGCTTGGTTTCATTGCTGGGCTTGTTGCCTTAGCTCTAT	
	GCGTCTTCTTCATACTGTGCTGCACTGGTTGTGGCACAAAC	
	TGTATGGGAAAACTTAAGTGTAATCGTTGTTGTGATAGAT	
	ACGAGGAATACGACCTCGAGCCGCATAAGGTTCATGTTCA	
	CTAA	
MERS S FL SPIKE 2cEMC/2012 (XBaI change (T to G)) (nucleotide)	ATGATACACTCAGTGTTTCTACTGATGTTCTTGTTAACACC	21
	TACAGAAAGTTACGTTGATGTAGGGCCAGATTCTGTTAAG	
	TCTGCTTGTATTGAGGTTGATATACAACAGACTTTCTTTGA	
	TAAAACTTGGCCTAGGCCAATTGATGTTTCTAAGGCTGAC	
	GGTATTATATACCCTCAAGGCCGTACATATTCTAACATAA	
	CTATCACTTATCAAGGTCTTTTTCCCTATCAGGGAGACCAT	
	GGTGATATGTATGTTTACTCTGCAGGACATGCTACAGGCA	
	CAACTCCACAAAAGTTGTTTGTAGCTAACTATTCTCAGGA	
	CGTCAAACAGTTTGCTAATGGGTTTGTCGTCCGTATAGGA	
	GCAGCTGCCAATTCCACTGGCACTGTTATTATTAGCCCATC	
	TACCAGCGCTACTATACGAAAAATTTACCCTGCTTTTATGC	
	TGGGTTCTTCAGTTGGTAATTTCTCAGATGGTAAAATGGG	
	CCGCTTCTTCAATCATACTCTAGTTCTTTTGCCCGATGGAT	
	GTGGCACTTTACTTAGAGCTTTTTATTGTATTCTGGAGCCT	
	CGCTCTGGAAATCATTGTCCTGCTGGCAATTCCTATACTTC	
	TTTTGCCACTTATCACACTCCTGCAACAGATTGTTCTGATG	
	GCAATTACAATCGTAATGCCAGTCTGAACTCTTTTAAGGA	
	GTATTTTAATTTACGTAACTGCACCTTTATGTACACTTATA	
	ACATTACCGAAGATGAGATTTTAGAGTGGTTTGGCATTAC	
	ACAAACTGCTCAAGGTGTTCACCTCTTCTCATCTCGGTATG	
	TTGATTTGTACGGCGGCAATATGTTTCAATTTGCCACCTTG	
	CCTGTTTATGATACTATTAAGTATTATTCTATCATTCCTCA	
	CAGTATTCGTTCTATCCAAAGTGATAGAAAAGCTTGGGCT	
	GCCTTCTACGTATATAAACTTCAACCGTTAACTTTCCTGTT	
	GGATTTTTCTGTTGATGGTTATATACGCAGAGCTATAGACT	
	GTGGTTTTAATGATTTGTCACAACTCCACTGCTCATATGAA	
	TCCTTCGATGTTGAATCTGGAGTTTATTCAGTTTCGTCTTT	
	CGAAGCAAAACCTTCTGGCTCAGTTGTGGAACAGGCTGAA	
	GGTGTTGAATGTGATTTTTCACCTCTTCTGTCTGGCACACC	
	TCCTCAGGTTTATAATTTCAAGCGTTTGGTTTTTACCAATT	
	GCAATTATAATCTTACCAAATTGCTTTCACTTTTTTCTGTG	
	AATGATTTTACTTGTAGTCAAATATCTCCAGCAGCAATTGC	
	TAGCAACTGTTATTCTTCACTGATTTTGGATTACTTTTCAT	
	ACCCACTTAGTATGAAATCCGATCTCAGTGTTAGTTCTGCT	
	GGTCCAATATCCCAGTTTAATTATAAACAGTCCTTTTCTAA	
	TCCCACATGTTTGATTTTAGCGACTGTTCCTCATAACCTTA	
	CTACTATTACTAAGCCTCTTAAGTACAGCTATATTAACAA	
	GTGCTCTCGTCTTCTTTCTGATGATCGTACTGAAGTACCTC	
	AGTTAGTGAACGCTAATCAATACTCACCCTGTGTATCCATT	
	GTCCCATCCACTGTGTGGGAAGACGGTGATTATTATAGGA	
	AACAACTATCTCCACTTGAAGGTGGTGGCTGGCTTGTTGC	
	TAGTGGCTCAACTGTTGCCATGACTGAGCAATTACAGATG	
	GGCTTTGGTATTACAGTTCAATATGGTACAGACACCAATA	
	GTGTTTGCCCCAAGCTTGAATTTGCTAATGACACAAAAAT	
	TGCCTCTCAATTAGGCAATTGCGTGGAATATTCCCTCTATG	
	GTGTTTCGGGCCGTGGTGTTTTTCAGAATTGCACAGCTGTA	
	GGTGTTCGACAGCAGCGCTTTGTTTATGATGCGTACCAGA	
	ATTTAGTTGGCTATTATTCTGATGATGGCAACTACTACTGT	
	TTGCGTGCTTGTGTTAGTGTTCCTGTTTCTGTCATCTATGAT	
	AAAGAAACTAAAACCCACGCTACTCTATTTGGTAGTGTTG	
	CATGTGAACACATTTCTTCTACCATGTCTCAATACTCCCGT	
	TCTACGCGATCAATGCTTAAACGGCGAGATTCTACATATG	
	GCCCCCTTCAGACACCTGTTGGTTGTGTCCTAGGACTTGTT	
	AATTCCTCTTTGTTCGTAGAGGACTGCAAGTTGCCTCTTGG	
	TCAATCTCTCTGTGCTCTTCCTGACACACCTAGTACTCTCA	

TABLE 10-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
	CACCTCGCAGTGTGCGCTCTGTTCCAGGTGAAATGCGCTT	
	GGCATCCATTGCTTTTAATCATCCTATTCAGGTTGATCAAC	
	TTAATAGTAGTTATTTTAAATTAAGTATACCCACTAATTTT	
	TCCTTTGGTGTGACTCAGGAGTACATTCAGACAACCATTC	
	AGAAAGTTACTGTTGATTGTAAACAGTACGTTTGCAATGG	
	TTTCCAGAAGTGTGAGCAATTACTGCGCGAGTATGGCCAG	
	TTTTGTTCCAAAATAAACCAGGCTCTCCATGGTGCCAATTT	
	ACGCCAGGATGATTCTGTACGTAATTTGTTTGCGAGCGTG	
	AAAAGCTCTCAATCATCTCCTATCATACCAGGTTTTGGAG	
	GTGACTTTAATTTGACACTTCTGGAACCTGTTTCTATATCT	
	ACTGGCAGTCGTAGTGCACGTAGTGCTATTGAGGATTTGC	
	TATTTGACAAAGTCACTATAGCTGATCCTGGTTATATGCA	
	AGGTTACGATGATTGCATGCAGCAAGGTCCAGCATCAGCT	
	CGTGATCTTATTTGTGCTCAATATGTGGCTGGTTACAAAGT	
	ATTACCTCCTCTTATGGATGTTAATATGGAAGCCGCGTATA	
	CTTCATCTTTGCTTGGCAGCATAGCAGGTGTTGGCTGGACT	
	GCTGGCTTATCCTCCTTTGCTGCTATTCCATTTGCACAGAG	
	TATCTTTTATAGGTTAAACGGTGTTGGCATTACTCAACAGG	
	TTCTTTCAGAGAACCAAAAGCTTATTGCCAATAAGTTTAA	
	TCAGGCTCTGGGAGCTATGCAAACAGGCTTCACTACAACT	
	AATGAAGCTTTTCAGAAGGTTCAGGATGCTGTGAACAACA	
	ATGCACAGGCTCTATCCAAATTAGCTAGCGAGCTATCTAA	
	TACTTTTGGTGCTATTTCCGCCTCTATTGGAGACATCATAC	
	AACGTCTTGATGTTCTCGAACAGGACGCCCAAATAGACAG	
	ACTTATTAATGGCCGTTTGACAACACTAAATGCTTTTGTTG	
	CACAGCAGCTTGTTCGTTCCGAATCAGCTGCTCTTTCCGCT	
	CAATTGGCTAAAGATAAAGTCAATGAGTGTGTCAAGGCAC	
	AATCCAAGCGTTCTGGATTTTGCGGTCAAGGCACACATAT	
	AGTGTCCTTTGTTGTAAATGCCCCTAATGGCCTTTACTTCA	
	TGCATGTTGGTTATTACCCTAGCAACCACATTGAGGTTGTT	
	TCTGCTTATGGTCTTTGCGATGCAGCTAACCCTACTAATTG	
	TATAGCCCCTGTTAATGGCTACTTTATTAAAACTAATAACA	
	CTAGGATTGTTGATGAGTGGTCATATACTGGCTCGTCCTTC	
	TATGCACCTGAGCCCATTACCTCCCTTAATACTAAGTATGT	
	TGCACCACAGGTGACATACCAAAACATTTCTACTAACCTC	
	CCTCCTCCTCTTCTCGGCAATTCCACCGGGATTGACTTCCA	
	AGATGAGTTGGATGAGTTTTTCAAAAATGTTAGCACCAGT	
	ATACCTAATTTTGGTTCCCTAACACAGATTAATACTACATT	
	ACTCGATCTTACCTACGAGATGTTGTCTCTTCAACAAGTTG	
	TTAAAGCCCTTAATGAGTCTTACATAGACCTTAAAGAGCT	
	TGGCAATTATACTTATTACAACAAATGGCCGTGGTACATT	
	TGGCTTGGTTTCATTGCTGGGCTTGTTGCCTTAGCTCTATG	
	CGTCTTCTTCATACTGTGCTGCACTGGTTGTGGCACAAACT	
	GTATGGGAAAACTTAAGTGTAATCGTTGTTGTGATAGATA	
	CGAGGAATACGACCTCGAGCCGCATAAGGTTCATGTTCAC	
	TAA	
Novel_MERS_S2_sub-unit_trimeric vaccine (nucleotide)	ATGATCCACTCCGTGTTCCTCCTCATGTTCCTGTTGACCCC	22
	CACTGAGTCAGACTGCAAGCTCCCGCTGGGACAGTCCCTG	
	TGTGCGCTGCCTGACACTCCTAGCACTCTGACCCCACGCTC	
	CGTGCGGTCGGTGCCTGGCGAAATGCGGCTGGCCTCCATC	
	GCCTTCAATCACCCAATCCAAGTGGATCAGCTGAATAGCT	
	CGTATTTCAAGCTGTCCATCCCCACGAACTTCTCGTTCGGG	
	GTCACCCAGGAGTACATCCAGACCACAATTCAGAAGGTCA	
	CCGTCGATTGCAAGCAATACGTGTGCAACGGCTTCCAGAA	
	GTGCGAGCAGCTGCTGAGAGAATACGGGCAGTTTTGCAGC	
	AAGATCAACCAGGCGCTGCATGGAGCTAACTTGCGCCAGG	
	ACGACTCCGTGCGCAACCTCTTTGCCTCTGTGAAGTCATCC	
	CAGTCCTCCCCAATCATCCCGGGATTCGGAGGGGACTTCA	
	ACCTGACCCTCCTGGAGCCCGTGTCGATCAGCACCGGTAG	
	CAGATCGGCGCGCTCAGCCATTGAAGATCTTCTGTTCGAC	
	AAGGTCACCATCGCCGATCCGGGCTACATGCAGGGATACG	
	ACGACTGTATGCAGCAGGGACCAGCCTCCGCGAGGGACCT	
	CATCTGCGCGCAATACGTGGCCGGGTACAAAGTGCTGCCT	
	CCTCTGATGGATGTGAACATGGAGGCCGCTTATACTTCGT	
	CCCTGCTCGGCTCTATCGCCGGCGTGGGGTGGACCGCCGG	
	CCTGTCCTCCTTCGCCGCTATCCCCTTTGCACAATCCATTT	
	TCTACCGGCTCAACGGCGTGGGCATTACTCAACAAGTCCT	
	GTCGGAGAACCAGAAGTTGATCGCAAACAAGTTCAATCA	
	GGCCCTGGGGGCCATGCAGACTGGATTCACTACGACTAAC	
	GAAGCGTTCCAGAAGGTCCAGGACGCTGTGAACAACAAC	
	GCCCAGGCGCTCTCAAAGCTGGCCTCCGAACTCAGCAACA	
	CCTTCGGAGCCATCAGCGCATCGATCGGTGACATAATTCA	
	GCGGCTGGACGTGCTGGAGCAGGACGCCCAGATCGACCG	
	CCTCATCAACGGACGGCTGACCACCTTGAATGCCTTCGTG	
	GCACAACAGCTGGTCCGGAGCGAATCAGCGGCACTTTCCG	
	CCCAACTCGCCAAGGACAAAGTCAACGAATGCGTGAAGG	

TABLE 10-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
	CCCAGTCCAAGAGGTCCGGTTTCTGCGGTCAAGGAACCCA	
	TATTGTGTCCTTCGTCGTGAACGCGCCCAACGGTCTGTACT	
	TTATGCACGTCGGCTACTACCCGAGCAATCATATCGAAGT	
	GGTGTCCGCCTACGGCCTGTGCGATGCCGCTAACCCCACT	
	AACTGTATTGCCCCTGTGAACGGATATTTTATTAAGACCA	
	ACAACACCCGCATTGTGGACGAATGGTCATACACCGGTTC	
	GTCCTTCTACGCGCCCGAGCCCATCACTTCACTGAACACC	
	AAATACGTGGCTCCGCAAGTGACCTACCAGAACATCTCCA	
	CCAATTTGCCGCCGCCGCTGCTCGGAAACAGCACCGGAAT	
	TGATTTCCAAGATGAACTGGACGAATTCTTCAAGAACGTG	
	TCCACTTCCATTCCCAACTTCGGAAGCCTGACACAGATCA	
	ACACCACCCTTCTCGACCTGACCTACGAGATGCTGAGCCT	
	TCAACAAGTGGTCAAGGCCCTGAACGAGAGCTACATCGAC	
	CTGAAGGAGCTGGGCAACTATACCTACTACAACAAGTGGC	
	CGGACAAGATTGAGGAGATTCTGTCGAAAATCTACCACAT	
	TGAAAACGAGATCGCCAGAATCAAGAAGCTTATCGGCGA	
	AGCC	
MERS_S0_Full-length Spike protein (nucleotide, codon optimized)	ATGGAAACCCCTGCCCAGCTGCTGTTCCTGCTGCTGCTGTG	23
	GCTGCCTGATACCACCGGCAGCTATGTGGACGTGGGCCCC	
	GATAGCGTGAAGTCCGCCTGTATCGAAGTGGACATCCAGC	
	AGACCTTTTTCGACAAGACCTGGCCCAGACCCATCGACGT	
	GTCCAAGGCCGACGGCATCATCTATCCACAAGGCCGGACC	
	TACAGCAACATCACCATTACCTACCAGGGCCTGTTCCCAT	
	ATCAAGGCGACCACGGCGATATGTACGTGTACTCTGCCGG	
	CCACGCCACCGGCACCACACCCCAGAAACTGTTCGTGGCC	
	AACTACAGCCAGGACGTGAAGCAGTTCGCCAACGGCTTCG	
	TCGTGCGGATTGGCGCCGCTGCCAATAGCACCGGCACAGT	
	GATCATCAGCCCCAGCACCAGCGCCACCATCCGGAAGATC	
	TACCCCGCCTTCATGCTGGGCAGCTCCGTGGGCAATTTCA	
	GCGACGGCAAGATGGGCCGGTTCTTCAACCACACCCTGGT	
	GCTGCTGCCCGATGGCTGTGGCACACTGCTGAGAGCCTTC	
	TACTGCATCCTGGAACCCAGAAGCGGCAACCACTGCCCTG	
	CCGGCAATAGCTACACCAGCTTCGCCACCTACCACACACC	
	CGCCACCGATTGCTCCGACGGCAACTACAACCGGAACGCC	
	AGCCTGAACAGCTTCAAAGAGTACTTCAACCTGCGGAACT	
	GCACCTTCATGTACACCTACAATATCACCGAGGACGAGAT	
	CCTGGAATGGTTCGGCATCACCCAGACCGCCCAGGGCGTG	
	CACCTGTTCAGCAGCAGATACGTGGACCTGTACGGCGGCA	
	ACATGTTCCAGTTTGCCACCCTGCCCGTGTACGACACCATC	
	AAGTACTACAGCATCATCCCCCACAGCATCCGGTCCATCC	
	AGAGCGACAGAAAAGCCTGGGCCGCCTTCTACGTGTACAA	
	GCTGCAGCCCCTGACCTTCCTGCTGGACTTCAGCGTGGAC	
	GGCTACATCAGACGGGCCATCGACTGCGGCTTCAACGACC	
	TGAGCCAGCTGCACTGCTCCTACGAGAGCTTCGACGTGGA	
	AAGCGGCGTGTACAGCGTGTCCAGCTTCGAGGCCAAGCCT	
	AGCGGCAGCGTGGTGGAACAGGCTGAGGGCGTGGAATGC	
	GACTTCAGCCCTCTGCTGAGCGGCACCCCTCCCCAGGTGT	
	ACAACTTCAAGCGGCTGGTGTTCACCAACTGCAATTACAA	
	CCTGACCAAGCTGCTGAGCCTGTTCTCCGTGAACGACTTC	
	ACCTGTAGCCAGATCAGCCCTGCCGCCATTGCCAGCAACT	
	GCTACAGCAGCCTGATCCTGGACTACTTCAGCTACCCCCT	
	GAGCATGAAGTCCGATCTGAGCGTGTCCTCCGCCGGACCC	
	ATCAGCCAGTTCAACTACAAGCAGAGCTTCAGCAACCCTA	
	CCTGCCTGATTCTGGCCACCGTGCCCCACAATCTGACCAC	
	CATCACCAAGCCCCTGAAGTACAGCTACATCAACAAGTGC	
	AGCAGACTGCTGTCCGACGACCGGACCGAAGTGCCCCAGC	
	TCGTGAACGCCAACCAGTACAGCCCCTGCGTGTCCATCGT	
	GCCCAGCACCGTGTGGGAGGACGGCGACTACTACAGAAA	
	GCAGCTGAGCCCCCTGGAAGGCGGCGGATGGCTGGTGGCT	
	TCTGGAAGCACAGTGGCCATGACCGAGCAGCTGCAGATG	
	GGCTTTGGCATCACCGTGCAGTACGGCACCGACACCAACA	
	GCGTGTGCCCCAAGCTGGAATTCGCCAATGACACCAAGAT	
	CGCCAGCCAGCTGGGAAACTGCGTGGAATACTCCCTGTAT	
	GGCGTGTCCGGACGGGGCGTGTTCCAGAATTGCACAGCAG	
	TGGGAGTGCGGCAGCAGAGATTCGTGTACGATGCCTACCA	
	GAACCTCGTGGGCTACTACAGCGACGACGGCAATTACTAC	
	TGCCTGCGGGCCTGTGTGTCCGTGCCCGTGTCCGTGATCTA	
	CGACAAAGAGACAAAGACCCACGCCACACTGTTCGGCTCC	
	GTGGCCTGCGAGCACATCAGCTCCACCATGAGCCAGTACT	
	CCCGCTCCACCCGGTCCATGCTGAAGCGGAGAGATAGCAC	
	CTACGGCCCCCTGCAGACACCTGTGGGATGTGTGCTGGGC	
	CTCGTGAACAGCTCCCTGTTTGTGGAAGATTGCAAGCTGC	
	CCCTGGGCCAGAGCCTGTGTGCCCTGCCAGATACCCCTAG	
	CACCCTGACCCCTAGAAGCGTGCGCTCTGTGCCCGGCGAA	
	ATGCGGCTGGCCTCTATCGCCTTCAATCACCCCATCCAGGT	
	GGACCAGCTGAACTCCAGCTACTTCAAGCTGAGCATCCCC	

TABLE 10-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
	ACCAACTTCAGCTTCGGCGTGACCCAGGAGTACATCCAGA	
	CCACAATCCAGAAAGTGACCGTGGACTGCAAGCAGTACGT	
	GTGCAACGGCTTTCAGAAGTGCGAACAGCTGCTGCGCGAG	
	TACGGCCAGTTCTGCAGCAAGATCAACCAGGCCCTGCACG	
	GCGCCAACCTGAGACAGGATGACAGCGTGCGGAACCTGTT	
	CGCCAGCGTGAAAAGCAGCCAGTCCAGCCCCATCATCCCT	
	GGCTTCGGCGGCGACTTTAACCTGACCCTGCTGGAACCTG	
	TGTCCATCAGCACCGGCTCCAGAAGCGCCAGATCCGCCAT	
	CGAGGACCTGCTGTTCGACAAAGTGACCATTGCCGACCCC	
	GGCTACATGCAGGGCTACGACGATTGCATGCAGCAGGGCC	
	CAGCCAGCGCCAGGGATCTGATCTGTGCCCAGTATGTGGC	
	CGGCTACAAGGTGCTGCCCCCCCCTGATGGACGTGAACATG	
	GAAGCCGCCTACACCTCCAGCCTGCTGGGCTCTATTGCTG	
	GCGTGGGATGGACAGCCGGCCTGTCTAGCTTTGCCGCCAT	
	CCCTTTCGCCCAGAGCATCTTCTACCGGCTGAACGGCGTG	
	GGCATCACACAACAGGTGCTGAGCGAGAACCAGAAGCTG	
	ATCGCCAACAAGTTTAACCAGGCACTGGGCGCCATGCAGA	
	CCGGCTTCACCACCACCAACGAGGCCTTCAGAAAGGTGCA	
	GGACGCCGTGAACAACAACGCCCAGGCTCTGAGCAAGCT	
	GGCCTCCGAGCTGAGCAATACCTTCGGCGCCATCAGCGCC	
	TCCATCGGCGACATCATCCAGCGGCTGGACGTGCTGGAAC	
	AGGACGCCCAGATCGACCGGCTGATCAACGGCAGACTGA	
	CCACCCTGAACGCCTTCGTGGCACAGCAGCTCGTGCGGAG	
	CGAATCTGCCGCTCTGTCTGCTCAGCTGGCCAAGGACAAA	
	GTGAACGAGTGCGTGAAGGCCCAGTCCAAGCGGAGCGGC	
	TTTTGTGGCCAGGGCACCCACATCGTGTCCTTCGTCGTGAA	
	TGCCCCCAACGGCCTGTACTTTATGCACGTGGGCTATTACC	
	CCAGCAACCACATCGAGGTGGTGTCCGCCTATGGCCTGTG	
	CGACGCCGCCAATCCTACCAACTGTATCGCCCCCGTGAAC	
	GGCTACTTCATCAAGACCAACAACACCCGGATCGTGGACG	
	AGTGGTCCTACACAGGCAGCAGCTTCTACGCCCCCGAGCC	
	CATCACCTCCCTGAACACCAAATACGTGGCCCCCCAAGTG	
	ACATACCAGAACATCTCCACCAACCTGCCCCCTCCACTGC	
	TGGGAAATTCCACCGGCATCGACTTCCAGGACGAGCTGGA	
	CGAGTTCTTCAAGAACGTGTCCACCTCCATCCCCAACTTCG	
	GCAGCCTGACCCAGATCAACACCACTCTGCTGGACCTGAC	
	CTACGAGATGCTGTCCCTGCAACAGGTCGTGAAAGCCCTG	
	AACGAGAGCTACATCGACCTGAAAGAGCTGGGGAACTAC	
	ACCTACTACAACAAGTGGCCTTGGTACATTTGGCTGGGCT	
	TTATCGCCGGCCTGGTGGCCCTGGCCCTGTGCGTGTTCTTC	
	ATCCTGTGCTGCACCGGCTGCGGCACCAATTGCATGGGCA	
	AGCTGAAATGCAACCGGTGCTGCGACAGATACGAGGAAT	
	ACGACCTGGAACCTCACAAAGTGCATGTGCAC	
	Betacoronavirus mRNA Sequences	
gb|KJ156934.1|: 21405-25466 Middle East respiratory syndrome coronavirus isolate Riyadh_14_2013, spike protein (nucleotide)	AUGAUACACUCAGUGUUUCUACUGAUGUUCUUGUUAAC	65
	ACCUACAGAAAGUUACGUUGAUGUAGGGCCAGAUUCUG	
	UUAAGUCUGCUUGUAUUGAGGUUGAUAUACAACAGACC	
	UUCUUUGAUAAAACUUGGCCUAGGCCAAUUGAUGUUUC	
	UAAGGCUGACGGUAUUAUAUACCCUCAAGGCCGUACAU	
	AUUCUAACAUAACUAUCACUUAUCAAGGUCUUUUUCCCU	
	AUCAGGGAGACCAUGGUGAUAUGUAUGUUUACUCUGCA	
	GGACAUGCUACAGGCACAACUCCACAAAAGUUGUUUGU	
	AGCUAACUAUUCUCAGGACGUCAAACAGUUUGCUAAUG	
	GGUUUGUCGUCCGUAUAGGAGCAGCUGCCAAUUCCACUG	
	GCACUGUUAUUAUUAGCCCAUCUACCAGCGCUACUAUAC	
	GAAAAAUUUACCCUGCUUUUAUGCUGGGUUCUUCAGUU	
	GGUAAUUUCUCAGAUGGUAAAAUGGGCCGCUUCUUCAA	
	UCAUACUCUAGUUCUUUUGCCCGAUGGAUGUGGCACUU	
	UACUUAGAGCUUUUUAUUGUAUUCUAGAGCCUCGCUCU	
	GGAAAUCAUUGUCCUGCUGGCAAUUCCUAUACUUCUUU	
	UGCCACUUAUCACACUCCUGCAACAGAUUGUUCUGAUGG	
	CAAUUACAAUCGUAAUGCCAGUCUGAACUCUUUUAAGG	
	AGUAUUUUAAUUUACGUAACUGCACCUUUAUGUACACU	
	UAUAACAUUACCGAAGAUGAGAUUUUAGAGUGGUUUGG	
	CAUUACACAAACUGCUCAAGGUGUUCACCUCUUCUCAUC	
	UCGGUAUGUUGAUUUGUACGGCGGCAAUAUGUUUCAAU	
	UUGCCACCUUGCCUGUUUAUGAUACUAUUAAGUAUUAU	
	UCUAUCAUUCCUCACAGUAUUCGUUCUAUCCAAAGUGAU	
	AGAAAAGCUUGGGCUGCCUUCUACGUAUAUAAACUUCA	
	ACCGUUAACUUUCCUGUUGGAUUUUUCUGUUGAUGGUU	
	AUAUACGCAGAGCUAUAGACUGUGGUUUUAAUGAUUUG	
	UCACAACUCCACUGCUCAUAUGAAUCCUUCGAUGUUGAA	
	UCUGGAGUUUAUUCAGUUUCGUCUUUCGAAGCAAAACC	
	UUCUGGCUCAGUUGUGGAACAGGCUGAAGGUGUUGAAU	
	GUGAUUUUUCACCUCUUCUGUCUGGCACACCUCCUCAGG	

TABLE 10-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
	UUUAUAAUUUCAAGCGUUUGGUUUUUACCAAUUGCAAU	
	UAUAAUCUUACCAAAUUGCUUUCACUUUUUUCUGUGAA	
	UGAUUUUACUUGUAGUCAAAUAUCUCCAGCAGCAAUUG	
	CUAGCAACUGUUAUUCUUCACUGAUUUUGGAUUAUUUU	
	UCAUACCCACUUAGUAUGAAAUCCGAUCUCAGUGUUAG	
	UUCUGCUGGUCCAAUAUCCCAGUUUAAUUAUAAACAGU	
	CCUUUUCUAAUCCCACAUGUUUGAUCUUAGCGACUGUUC	
	CUCAUAACCUUACUACUAUUACUAAGCCUCUUAAGUACA	
	GCUAUAUUAACAAGUGCUCUCGUCUUCUUUCUGAUGAU	
	CGUACUGAAGUACCUCAGUUAGUGAACGCUAAUCAAUA	
	CUCACCCUGUGUAUCCAUUGUCCCAUCCACUGUGUGGGA	
	AGACGGUGAUUAUUAUAGGAAACAACUAUCUCCACUUG	
	AAGGUGGUGGCUGGCUUGUUGCUAGUGGCUCAACUGUU	
	GCCAUGACUGAGCAAUUACAGAUGGGCUUUGGUAUUAC	
	AGUUCAAUAUGGUACAGACACCAAUAGUGUUUGCCCCA	
	AGCUUGAAUUUGCUAAUGACACAAAAAUUGCCUCUCAA	
	UUAGGCAAUUGCGUGGAAUAUUCCCUCUAUGGUGUUUC	
	GGGCCGUGGUGUUUUUCAGAAUUGCACAGCUGUAGGUG	
	UUCGACAGCAGCGCUUUGUUUAUGAUGCGUACCAGAAU	
	UUAGUUGGCUAUUAUUCUGAUGAUGGCAACUACUACUG	
	UCUGCGUGCUUGUGUUAGUGUUCCUGUUUCUGUCAUCU	
	AUGAUAAAGAAACUAAAACCCACGCUACUCUAUUUGGU	
	AGUGUUGCAUGUGAACACAUUUCUUCUACCAUGUCUCA	
	AUACUCCCGUUCUACGCGAUCAAUGCUUAAACGGCGAGA	
	UUCUACAUAUGGCCCCCUUCAGACACCUGUUGGUUGUGU	
	CCUAGGACUUGUUAAUUCCUCUUUGUUCGUAGAGGACU	
	GCAAGUUGCCUCUCGGUCAAUCUCUCUGUGCUCUUCCUG	
	ACACACCUAGUACUCUCACACCUCGCAGUGUGCGCUCUG	
	UGCCAGGUGAAAUGCGCUUGGCAUCCAUUGCUUUUAAU	
	CAUCCCAUUCAGGUUGAUCAACUUAAUAGUAGUUAUUU	
	UAAAUUAAGUAUACCCACUAAUUUUUCCUUUGGUGUGA	
	CUCAGGAGUACAUUCAGACAACCAUUCAGAAAGUUACU	
	GUUGAUUGUAAACAGUACGUUUGCAAUGGUUUCCAGAA	
	GUGUGAGCAAUUACUGCGCGAGUAUGGCCAGUUUUGUU	
	CCAAAAUAAACCAGGCUCUCCAUGGUGCCAAUUUACGCC	
	AGGAUGAUUCUGUACGUAAUUUGUUUGCGAGCGUGAAA	
	AGCUCUCAAUCAUCUCCUAUCAUACCAGGUUUUGGAGGU	
	GACUUUAAUUUGACACUUCUAGAACCUGUUUCUAUAUC	
	UACUGGCAGUCGUAGUGCACGUAGUGCUAUUGAGGAUU	
	UGCUAUUUGACAAAGUCACUAUAGCUGAUCCUGGUUAU	
	AUGCAAGGUUACGAUGAUUGUAUGCAGCAAGGUCCAGC	
	AUCAGCUCGUGAUCUUAUUUGUGCUCAAUAUGUGGCUG	
	GUUAUAAAGUAUUACCUCCUCUUAUGGAUGUUAAUAUG	
	GAAGCCGCGUAUACUUCAUCUUUGCUUGGCAGCAUAGCA	
	GGUGUUGGCUGGACUGCUGGCUUAUCCUCCUUUGCUGCU	
	AUUCCAUUUGCACAGAGUAUYUUUUAUAGGUUAAACGG	
	UGUUGGCAUUACUCAACAGGUUCUUUCAGAGAACCAAA	
	AGCUUAUUGCCAAUAAGUUUAAUCAGGCUCUGGGAGCU	
	AUGCAAACAGGCUUCACUACAACUAAUGAAGCUUUUCG	
	GAAGGUUCAGGAUGCUGUGAACAACAAUGCACAGGCUC	
	UAUCCAAAUUAGCUAGCGAGCUAUCUAAUACUUUUGGU	
	GCUAUUUCCGCCUCUAUUGGAGACAUCAUACAACGUCUU	
	GAUGUUCUCGAACAGGACGCCCAAAUAGACAGACUUAU	
	UAAUGGCCGUUUGACAACACUAAAUGCUUUUGUUGCAC	
	AGCAGCUUGUUCGUUCCGAAUCAGCUGCUCUUUCCGCUC	
	AAUUGGCUAAAGAUAAAGUCAAUGAGUGUGUCAAGGCA	
	CAAUCCAAGCGUUCUGGAUUUUGCGGUCAAGGCACACAU	
	AUAGUGUCCUUUGUUGUAAAUGCCCCUAAUGGCCUUUA	
	CUUUAUGCAUGUUGGUUAUUACCCUAGCAACCACAUUG	
	AGGUUGUUUCUGCUUAUGGUCUUUGCGAUGCAGCUAAC	
	CCUACUAAUUGUAUAGCCCCUGUUAAUGGCUACUUUAU	
	UAAAACUAAUAACACUAGGAUUGUUGAUGAGUGGUCAU	
	AUACUGGCUCGUCCUUCUAUGCACCUGAGCCCAUCACCU	
	CUCUUAAUACUAAGUAUGUUGCACCACAGGUGACAUACC	
	AAAACAUUUCUACUAACCUCCCUCCUCCUCUUCUCGGCA	
	AUUCCACCGGGAUUGACUUCCAAGAUGAGUUGGAUGAG	
	UUUUUCAAAAAUGUUAGCACCAGUAUACCUAAUUUUGG	
	UUCUCUAACACAGAUUAAUACUACAUUACUCGAUCUUAC	
	CUACGAGAUGUUGUCUCUUCAACAAGUUGUUAAAGCCC	
	UUAAUGAGUCUUACAUAGACCUUAAAGAGCUUGGCAAU	
	UAUACUUAUUACAACAAAUGGCCGUGGUACAUUUGGCU	
	UGGUUUCAUUGCUGGGCUUGUUGCCUUAGCUCUAUGCG	
	UCUUCUUCAUACUGUGCUGCACUGGUUGUGGCACAAACU	
	GUAUGGGAAAACUUAAGUGUAAUCGUUGUUGUGAUAGA	
	UACGAGGAAUACGACCUCGAGCCGCAUAAGGUUCAUGU	
	UCACUAA	

TABLE 10-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
MERS S FL SPIKE 2cEMC/2012 (XBaI change (U to G)) (nucleotide)	AUGAUACACUCAGUGUUUCUACUGAUGUUCUUGUUAAC	66
	ACCUACAGAAAGUUACGUUGAUGUAGGGCCAGAUUCUG	
	UUAAGUCUGCUUGUAUUGAGGUUGAUAUACAACAGACU	
	UUCUUUGAUAAAACUUGGCCUAGGCCAAUUGAUGUUUC	
	UAAGGCUGACGGUAUUAUAUACCCUCAAGGCCGUACAU	
	AUUCUAACAUAACUAUCACUUAUCAAGGUCUUUUUCCCU	
	AUCAGGGAGACCAUGGUGAUAUGUAUGUUUACUCUGCA	
	GGACAUGCUACAGGCACAACUCCACAAAAGUUGUUUGU	
	AGCUAACUAUUCUCAGGACGUCAAACAGUUUGCUAAUG	
	GGUUUGUCGUCCGUAUAGGAGCAGCUGCCAAUUCCACUG	
	GCACUGUUAUUAUUAGCCCAUCUACCAGCGCUACUAUAC	
	GAAAAAUUUACCCUGCUUUUAUGCUGGGUUCUUCAGUU	
	GGUAAUUUCUCAGAUGGUAAAAUGGGCCGCUUCUUCAA	
	UCAUACUCUAGUUCUUUUGCCCGAUGGAUGUGGCACUU	
	UACUUAGAGCUUUUUAUUGUAUUCUGGAGCCUCGCUCU	
	GGAAAUCAUUGUCCUGCUGGCAAUUCCUAUACUUCUUU	
	UGCCACUUAUCACACUCCUGCAACAGAUUGUUCUGAUGG	
	CAAUUACAAUCGUAAUGCCAGUCUGAACUCUUUUAAGG	
	AGUAUUUUAAUUUACGUAACUGCACCUUUAUGUACACU	
	UAUAACAUUACCGAAGAUGAGAUUUUAGAGUGGUUUGG	
	CAUUACACAAACUGCUCAAGGUGUUCACCUCUUCUCAUC	
	UCGGUAUGUUGAUUUGUACGGCGGCAAUAUGUUUCAAU	
	UUGCCACCUUGCCUGUUUAUGAUACUAUUAAGUAUUAU	
	UCUAUCAUUCCUCACAGUAUUCGUUCUAUCCAAAGUGAU	
	AGAAAAGCUUGGGCUGCCUUCUACGUAUAUAAACUUCA	
	ACCGUUAACUUUCCUGUUGGAUUUUUCUGUUGAUGGUU	
	AUAUACGCAGAGCUAUAGACUGUGGUUUUAAUGAUUUG	
	UCACAACUCCACUGCUCAUAUGAAUCCUUCGAUGUUGAA	
	UCUGGAGUUUAUUCAGUUUCGUCUUUCGAAGCAAAACC	
	UUCUGGCUCAGUUGUGGAACAGGCUGAAGGUGUUGAAU	
	GUGAUUUUUCACCUCUUCUGUCUGGCACACCUCCUCAGG	
	UUUAUAAUUUCAAGCGUUUGGUUUUUACCAAUUGCAAU	
	UAUAAUCUUACCAAAUUGCUUUCACUUUUUUCUGUGAA	
	UGAUUUUACUUGUAGUCAAAUAUCUCCAGCAGCAAUUG	
	CUAGCAACUGUUAUUCUUCACUGAUUUUGGAUUACUUU	
	UCAUACCCACUUAGUAUGAAAUCCGAUCUCAGUGUUAG	
	UUCUGCUGGUCCAAUAUCCCAGUUUAAUUAUAAACAGU	
	CCUUUUCUAAUCCCACAUGUUUGAUUUUAGCGACUGUUC	
	CUCAUAACCUUACUACUAUUACUAAGCCUCUUAAGUACA	
	GCUAUAUUAACAAGUGCUCUCGUCUUCUUUCUGAUGAU	
	CGUACUGAAGUACCUCAGUUAGUGAACGCUAAUCAAUA	
	CUCACCCUGUGUAUCCAUUGUCCCAUCCACUGUGUGGGA	
	AGACGGUGAUUAUUAUAGGAAACAACUAUCUCCACUUG	
	AAGGUGGUGGCUGGCUUGUUGCUAGUGGCUCAACUGUU	
	GCCAUGACUGAGCAAUUACAGAUGGGCUUUGGUAUUAC	
	AGUUCAAUAUGGUACAGACACCAAUAGUGUUUGCCCCA	
	AGCUUGAAUUUGCUAAUGACACAAAAAUUGCCUCUCAA	
	UUAGGCAAUUGCGUGGAAUAUUCCCUCUAUGGUGUUUC	
	GGGCCGUGGUGUUUUUCAGAAUUGCACAGCUGUAGGUG	
	UUCGACAGCAGCGCUUUGUUUAUGAUGCGUACCAGAAU	
	UUAGUUGGCUAUUAUUCUGAUGAUGGCAACUACUACUG	
	UUUGCGUGCUUGUGUUAGUGUUCCUGUUUCUGUCAUCU	
	AUGAUAAAGAAACUAAAACCCACGCUACUCUAUUUGGU	
	AGUGUUGCAUGUGAACACAUUUCUUCUACCAUGUCUCA	
	AUACUCCCGUUCUACGCGAUCAAUGCUUAAACGGCGAGA	
	UUCUACAUAUGGCCCCCUUCAGACACCUGUUGGUUGUGU	
	CCUAGGACUUGUUAAUUCCUCUUUGUUCGUAGAGGACU	
	GCAAGUUGCCUCUUGGUCAAUCUCUCUGUGCUCUUCCUG	
	ACACACCUAGUACUCUCACACCUCGCAGUGUGCGCUCUG	
	UUCCAGGUGAAAUGCGCUUGGCAUCCAUUGCUUUUAAU	
	CAUCCUAUUCAGGUUGAUCAACUUAAUAGUAGUUAUUU	
	UAAAUUAAGUAUACCCACUAAUUUUUCCUUUGGUGUGA	
	CUCAGGAGUACAUUCAGACAACCAUUCAGAAAGUUACU	
	GUUGAUUGUAAACAGUACGUUUGCAAUGGUUUCCAGAA	
	GUGUGAGCAAUUACUGCGCGAGUAUGGCCAGUUUUGUU	
	CCAAAAUAAACCAGGCUCUCCAUGGUGCCAAUUUACGCC	
	AGGAUGAUUCUGUACGUAAUUUGUUUGCGAGCGUGAAA	
	AGCUCUCAAUCAUCUCCUAUCAUACCAGGUUUUGGAGGU	
	GACUUUAAUUUGACACUUCUGGAACCUGUUUCUAUAUC	
	UACUGGCAGUCGUAGUGCACGUAGUGCUAUUGAGGAUU	
	UGCUAUUUGACAAAGUCACUAUAGCUGAUCCUGGUUAU	
	AUGCAAGGUUACGAUGAUUGCAUGCAGCAAGGUCCAGC	
	AUCAGCUCGUGAUCUUAUUUGUGCUCAAUAUGUGGCUG	
	GUUACAAAGUAUUACCUCCUCUUAUGGAUGUUAAUAUG	
	GAAGCCGCGUAUACUUCAUCUUUGCUUGGCAGCAUAGCA	
	GGUGUUGGCUGGACUGCUGGCUUAUCCUCCUUUGCUGCU	
	AUUCCAUUUGCACAGAGUAUCUUUUAUAGGUUAAACGG	

TABLE 10-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	AGCUUAUUGCCAAUAAGUUUAAUCAGGCUCUGGGAGCU	
	AUGCAAACAGGCUUCACUACAACUAAUGAAGCUUUUCA	
	GAAGGUUCAGGAUGCUGUGAACAACAAUGCACAGGCUC	
	UAUCCAAAUUAGCUAGCGAGCUAUCUAAUACUUUUGGU	
	GCUAUUUCCGCCUCUAUUGGAGACAUCAUACAACGUCUU	
	GAUGUUCUCGAACAGGACGCCCAAAUAGACAGACUUAU	
	UAAUGGCCGUUUGACAACACUAAAUGCUUUUGUUGCAC	
	AGCAGCUUGUUCGUUCCGAAUCAGCUGCUCUUUCCGCUC	
	AAUUGGCUAAAGAUAAAGUCAAUGAGUGUGUCAAGGCA	
	CAAUCCAAGCGUUCUGGAUUUUGCGGUCAAGGCACACAU	
	AUAGUGUCCUUUGUUGUAAAUGCCCCUAAUGGCCUUUA	
	CUUCAUGCAUGUUGGUUAUUACCCUAGCAACCACAUUGA	
	GGUUGUUUCUGCUUAUGGUCUUUGCGAUGCAGCUAACC	
	CUACUAAUUGUAUAGCCCCUGUUAAUGGCUACUUUAUU	
	AAAACUAAUAACACUAGGAUUGUUGAUGAGUGGUCAUA	
	UACUGGCUCGUCCUUCUAUGCACCUGAGCCCAUUACCUC	
	CCUUAAUACUAAGUAUGUUGCACCACAGGUGACAUACCA	
	AAACAUUUCUACUAACCUCCCCUCCUCCUCUUCUCGGCAA	
	UUCCACCGGGAUUGACUUCCAAGAUGAGUUGGAUGAGU	
	UUUUCAAAAAUGUUAGCACCAGUAUACCUAAUUUUGGU	
	UCCCUAACACAGAUUAAUACUACAUUACUCGAUCUUACC	
	UACGAGAUGUUGUCUCUUCAACAAGUUGUUAAAGCCCU	
	UAAUGAGUCUUACAUAGACCUUAAAGAGCUUGGCAAUU	
	AUACUUAUUACAACAAAUGGCCGUGGUACAUUUGGCUU	
	GGUUUCAUUGCUGGGCUUGUUGCCUUAGCUCUAUGCGU	
	CUUCUUCAUACUGUGCUGCACUGGUUGUGGCACAAACUG	
	UAUGGGAAAACUUAAGUGUAAUCGUUGUUGUGAUAGAU	
	ACGAGGAAUACGACCUCGAGCCGCAUAAGGUUCAUGUUC	
	ACUAA	
Novel_MERS_S2_sub-unit_trimeric vaccine (nucleotide)	AUGAUCCACUCCGUGUUCCUCCUCAUGUUCCUGUUGACC	67
	CCCACUGAGUCAGACUGCAAGCUCCCGCUGGGACAGUCC	
	CUGUGUGCGCUGCCUGACACUCCUAGCACUCUGACCCCA	
	CGCUCCGUGCGGUCGGUGCCUGGCGAAAUGCGGCUGGCC	
	UCCAUCGCCUUCAAUCACCCAAUCCAAGUGGAUCAGCUG	
	AAUAGCUCGUAUUUCAAGCUGUCCAUCCCCACGAACUUC	
	UCGUUCGGGGUCACCCAGGAGUACAUCCAGACCACAAUU	
	CAGAAGGUCACCGUCGAUUGCAAGCAAUACGUGUGCAAC	
	GGCUUCCAGAAGUGCGAGCAGCUGCUGAGAGAAUACGG	
	GCAGUUUUGCAGCAAGAUCAACCAGGCGCUGCAUGGAGC	
	UAACUUGCGCCAGGACGACUCCGUGCGCAACCUCUUUGC	
	CUCUGUGAAGUCAUCCCAGUCCUCCCCAAUCAUCCCGGG	
	AUUCGGAGGGGACUUCAACCUGACCCUCCUGGAGCCCGU	
	GUCGAUCAGCACCGGUAGCAGAUCGGCGCGCUCAGCCAU	
	UGAAGAUCUUCUGUUCGACAAGGUCACCAUCGCCGAUCC	
	GGGCUACAUGCAGGGAUACGACGACUGUAUGCAGCAGG	
	GACCAGCCUCCGCGAGGGACCUCAUCUGCGCGCAAUACG	
	UGGCCGGGUACAAAGUGCUGCCUCCUCUGAUGGAUGUG	
	AACAUGGAGGCCGCUUAUACUUCGUCCCUGCUCGGCUCU	
	AUCGCCGGCGUGGGGUGGACCGCCGGCCUGUCCUCCUUC	
	GCCGCUAUCCCCUUUGCACAAUCCAUUUUCUACCGGCUC	
	AACGGCGUGGGCAUUACUCAACAAGUCCUGUCGGAGAAC	
	CAGAAGUUGAUCGCAAACAAGUUCAAUCAGGCCCUGGG	
	GGCCAUGCAGACUGGAUUCACUACGACUAACGAAGCGUU	
	CCAGAAGGUCCAGGACGCUGUGAACAACAACGCCCAGGC	
	GCUCUCAAAGCUGGCCUCCGAACUCAGCAACACCUUCGG	
	AGCCAUCAGCGCAUCGAUCGGUGACAUAAUUCAGCGGCU	
	GGACGUGCUGGAGCAGGACGCCCAGAUCGACCGCCUCAU	
	CAACGGACGGCUGACCACCUUGAAUGCCUUCGUGGCACA	
	ACAGCUGGUCCGGAGCGAAUCAGCGGCACUUUCCGCCCA	
	ACUCGCCAAGGACAAAGUCAACGAAUGCGUGAAGGCCCA	
	GUCCAAGAGGUCCGGUUUCUGCGGUCAAGGAACCCAUAU	
	UGUGUCCUUCGUCGUGAACGCGCCCAACGGUCUGUACUU	
	UAUGCACGUCGGCUACUACCCGAGCAAUCAUAUCGAAGU	
	GGUGUCCGCCUACGGCCUGUGCGAUGCCGCUAACCCCAC	
	UAACUGUAUUGCCCCUGUGAACGGAUAUUUUAUUAAGA	
	CCAACAACACCCGCAUUGUGGACGAAUGGUCAUACACCG	
	GUUCGUCCUUCUACGCGCCCGAGCCCAUCACUUCACUGA	
	ACACCAAAUACGUGGCUCCGCAAGUGACCUACCAGAACA	
	UCUCCACCAAUUUGCCGCCGCCGCUGCUCGGAAACAGCA	
	CCGGAAUUGAUUUCCAAGAUGAACUGGACGAAUUCUUC	
	AAGAACGUGUCCACUUCCAUUCCCAACUUCGGAAGCCUG	
	ACACAGAUCAACACCACCCUUCUCGACCUGACCUACGAG	
	AUGCUGAGCCUUCAACAAGUGGUCAAGGCCCUGAACGAG	
	AGCUACAUCGACCUGAAGGAGCUGGGCAACUAUACCUAC	
	UACAACAAGUGGCCGGACAAGAUUGAGGAGAUUCUGUC	

TABLE 10-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
	GAAAAUCUACCACAUUGAAAACGAGAUCGCCAGAAUCA AGAAGCUUAUCGGCGAAGCC	
MERS_S0_Full-length Spike protein (nucleotide, codon optimized)	AUGGAAACCCCUGCCCAGCUGCUGUUCCUGCUGCUGCUG UGGCUGCCUGAUACCACCGGCAGCUAUGUGGACGUGGGC CCCGAUAGCGUGAAGUCCGCCUGUAUCGAAGUGGACAUC CAGCAGACCUUUUUCGACAAGACCUGGCCCAGACCCAUC GACGUGUCCAAGGCCGACGGCAUCAUCUAUCCACAAGGC CGGACCUACAGCAACAUCACCAUUACCUACCAGGGCCUG UUCCCAUAUCAAGGCGACCACGGCGAUAUGUACGUGUAC UCUGCCGGCCACGCCACCGGCACCACACCCCAGAAACUG UUCGUGGCCAACUACAGCCAGGACGUGAAGCAGUUCGCC AACGGCUUCGUCGUGCGGAUUGGCGCCGCUGCCAAUAGC ACCGGCACAGUGAUCAUCAGCCCCAGCACCAGCGCCACC AUCCGGAAGAUCUACCCCGCCUUCAUGCUGGGCAGCUCC GUGGGCAAUUUCAGCGACGGCAAGAUGGGCCGGUUCUU CAACCACACCCUGGUGCUGCUGCCCGAUGGCUGUGGCAC ACUGCUGAGAGCCUUCUACUGCAUCCUGGAACCCAGAAG CGGCAACCACUGCCCUGCCGGCAAUAGCUACACCAGCUU CGCCACCUACCACACACCCGCCACCGAUUGCUCCGACGG CAACUACAACCGGAACGCCAGCCUGAACAGCUUCAAAGA GUACUUCAACCUGCGGAACUGCACCUUCAUGUACACCUA CAAUAUCACCGAGGACGAGAUCCUGGAAUGGUUCGGCA UCACCCAGACCGCCCAGGGCGUGCACCUGUUCAGCAGCA GAUACGUGGACCUGUACGGCGGCAACAUGUUCCAGUUU GCCACCCUGCCCGUGUACGACACCAUCAAGUACUACAGC AUCAUCCCCCACAGCAUCCGGUCCAUCCAGAGCGACAGA AAAGCCUGGGCCGCCUUCUACGUGUACAAGCUGCAGCCC CUGACCUUCCUGCUGGACUUCAGCGUGGACGGCUACAUC AGACGGGCCAUCGACUGCGGCUUCAACGACCUGAGCCAG CUGCACUGCUCCUACGAGAGCUUCGACGUGGAAAGCGGC GUGUACAGCGUGUCCAGCUUCGAGGCCAAGCCUAGCGGC AGCGUGGUGGAACAGGCUGAGGGCGUGGAAUGCGACUU CAGCCCUCUGCUGAGCGGCACCCCUCCCCAGGUGUACAA CUUCAAGCGGCUGGUGUUCACCAACUGCAAUUACAACCU GACCAAGCUGCUGAGCCUGUUCUCCGUGAACGACUUCAC CUGUAGCCAGAUCAGCCCUGCCGCCAUUGCCAGCAACUG CUACAGCAGCCUGAUCCUGGACUACUUCAGCUACCCCCU GAGCAUGAAGUCCGAUCUGAGCGUGUCCUCCGCCGGACC CAUCAGCCAGUUCAACUACAAGCAGAGCUUCAGCAACCC UACCUGCCUGAUUCUGGCCACCGUGCCCCACAAUCUGAC CACCAUCACCAAGCCCCUGAAGUACAGCUACAUCAACAA GUGCAGCAGACUGCUGUCCGACGACCGGACCGAAGUGCC CCAGCUCGUGAACGCCAACCAGUACAGCCCCUGCGUGUC CAUCGUGCCCAGCACCGUGUGGGAGGACGGCGACUACUA CAGAAAGCAGCUGAGCCCCCUGGAAGGCGGCGGAUGGCU GGUGGCUUCUGGAAGCACAGUGGCCAUGACCGAGCAGCU GCAGAUGGGCUUUGGCAUCACCGUGCAGUACGGCACCGA CACCAACAGCGUGUGCCCCAAGCUGGAAUUCGCCAAUGA CACCAAGAUCGCCAGCCAGCUGGGAAACUGCGUGGAAUA CUCCCUGUAUGGCGUGUCCGGACGGGGCGUGUUCCAGAA UUGCACAGCAGUGGGAGUGCGGCAGCAGAGAUUCGUGU ACGAUGCCUACCAGAACCUCGUGGGCUACUACAGCGACG ACGGCAAUUACUACUGCCUGCGGGCCUGUGUGUCCGUGC CCGUGUCCGUGAUCUACGACAAAGAGACAAAGACCCACG CCACACUGUUCGGCUCCGUGGCCUGCGAGCACAUCAGCU CCACCAUGAGCCAGUACUCCCGCUCCACCCGGUCCAUGC UGAAGCGGAGAGAUAGCACCUACGGCCCCCUGCAGACAC CUGUGGGAUGUGUGCUGGGCCUCGUGAACAGCUCCCUGU UUGUGGAAGAUUGCAAGCUGCCCCUGGGCCAGAGCCUGU GUGCCCUGCCAGAUACCCCUAGCACCCUGACCCCUAGAA GCGUGCGCUCUGUGCCCGGCGAAAUGCGGCUGGCCUCUA UCGCCUUCAAUCACCCCAUCCAGGUGGACCAGCUGAACU CCAGCUACUUCAAGCUGAGCAUCCCCACCAACUUCAGCU UCGGCGUGACCCAGGAGUACAUCCAGACCACAAUCCAGA AAGUGACCGUGGACUGCAAGCAGUACGUGUGCAACGGC UUUCAGAAGUGCGAACAGCUGCUGCGCGAGUACGGCCAG UUCUGCAGCAAGAUCAACCAGGCCCUGCACGGCGCCAAC CUGAGACAGGAUGACAGCGUGCGGAACCUGUUCGCCAGC GUGAAAAGCAGCCAGUCCAGCCCCAUCAUCCCUGGCUUC GGCGGCGACUUUAACCUGACCCUGCUGGAACCUGUGUCC AUCAGCACCGGCUCCAGAAGCGCCAGAUCCGCCAUCGAG GACCUGCUGUUCGACAAAGUGACCAUUGCCGACCCCGGC UACAUGCAGGGCUACGACGAUUGCAUGCAGCAGGGCCCA GCCAGCGCCAGGGAUCUGAUCUGUGCCCAGUAUGUGGCC GGCUACAAGGUGCUGCCCCCCCCUGAUGGACGUGAACAUG GAAGCCGCCUACACCUCCAGCCUGCUGGGCUCUAUUGCU	68

TABLE 10-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
	GGCGUGGGAUGGACAGCCGGCCUGUCUAGCUUUGCCGCC	
	AUCCCUUUCGCCCAGAGCAUCUUCUACCGGCUGAACGGC	
	GUGGGCAUCACACAACAGGUGCUGAGCGAGAACCAGAA	
	GCUGAUCGCCAACAAGUUUAACCAGGCACUGGGCGCCAU	
	GCAGACCGGCUUCACCACCACCAACGAGGCCUUCAGAAA	
	GGUGCAGGACGCCGUGAACAACAACGCCCAGGCUCUGAG	
	CAAGCUGGCCUCCGAGCUGAGCAAUACCUUCGGCGCCAU	
	CAGCGCCUCCAUCGGCGACAUCAUCCAGCGGCUGGACGU	
	GCUGGAACAGGACGCCCAGAUCGACCGGCUGAUCAACGG	
	CAGACUGACCACCCUGAACGCCUUCGUGGCACAGCAGCU	
	CGUGCGGAGCGAAUCUGCCGCUCUGUCUGCUCAGCUGGC	
	CAAGGACAAAGUGAACGAGUGCGUGAAGGCCCAGUCCA	
	AGCGGAGCGGCUUUUGUGGCCAGGGCACCCACAUCGUGU	
	CCUUCGUCGUGAAUGCCCCCAACGGCCUGUACUUUAUGC	
	ACGUGGGCUAUUACCCCAGCAACCACAUCGAGGUGGUGU	
	CCGCCUAUGGCCUGUGCGACGCCGCCAAUCCUACCAACU	
	GUAUCGCCCCCGUGAACGGCUACUUCAUCAAGACCAACA	
	ACACCCGGAUCGUGGACGAGUGGUCCUACACAGGCAGCA	
	GCUUCUACGCCCCCGAGCCCAUCACCUCCCUGAACACCA	
	AAUACGUGGCCCCCCAAGUGACAUACCAGAACAUCUCCA	
	CCAACCUGCCCCCUCCACUGCUGGGAAAUUCCACCGGCA	
	UCGACUUCCAGGACGAGCUGGACGAGUUCUUCAAGAACG	
	UGUCCACCUCCAUCCCCAACUUCGGCAGCCUGACCCAGA	
	UCAACACCACUCUGCUGGACCUGACCUACGAGAUGCUGU	
	CCCUGCAACAGGUCGUGAAAGCCCUGAACGAGAGCUACA	
	UCGACCUGAAAGAGCUGGGGAACUACACCUACUACAACA	
	AGUGGCCUUGGUACAUUUGGCUGGGCUUUAUCGCCGGCC	
	UGGUGGCCCUGGCCCUGUGCGUGUUCUUCAUCCUGUGCU	
	GCACCGGCUGCGGCACCAAUUGCAUGGGCAAGCUGAAAU	
	GCAACCGGUGCUGCGACAGAUACGAGGAAUACGACCUGG	
	AACCUCACAAAGUGCAUGUGCAC	

TABLE 11

Betacoronavirus Amino Acid Sequences

Strain	Amino Acid Sequence	SEQ ID NO:
gb|KJ156934.1|: 21405-25466 Middle East respiratory syndrome coronavirus isolate Riyadh_14_2013, spike protein (amino acid)	MIHSVFLLMFLLTPTESYVDVGPDSVKSACIEVDIQQTFFDK TWPRPIDVSKADGIIYPQGRTYSNITITYQGLFPYQGDHGDM YVYSAGHATGTTpQKLFVANYSQDVKQFANGFVVRIGAAANS TGTVIISPSTSATIRKIYPAFMLGSSVGNFSDGKMGRFFNHT LVLLPDGCGTLLRAFYCILEPRSGNHCPAGNSYTSFATYHTP ATDCSDGNYNRNASLNSFKEYFNLRNCTFMYTYNITEDEILE WFGITQTAQGVHLFSSRYVDLYGGNMFQFATLPVYDTIKYYS IIPHSIRSIQSDRKAWAAFYVYKLQPLTFLLDFSVDGYIRRA IDCGFNDLSQLHCSYESFDVESGVYSVSSFEAKPSGSVVEQA EGVECDFSPLLSGTPPQVYNFKRLVFTNCNYNLTKLLSLFSV NDFtCSQISPAAIASNCYSSLILDYFSYPLSMKSDLSVSSAG PISQFNYKQSFSNPTCLILATVPHNLTTITKPLKYSYINKCS RLLSDDRTEVPQLVNANQYSPCVSIVPSTVWEDGDYYRKQLS PLEGGGWLVASGSTVAMTEQLQMGFGITVQYGTDTNSVCPKL EFANDTKIASQLGNCVEYSLYGVSGRGVFQNCTAVGVRQQRF VYDAYQNLVGYYSDDGNYYCLRACVSVPVSVIYDKETKTHAT LFGSVACEHISSTMSQYSRSTRSMLKRRDSTYGPLQTPVGCV LGLVNSSLFVEDCKLPLGQSLCALPDTPSTLTPRSVRSVPGE MRLASIAFNHPIQVDQLNSSYFKLSIPTNFSFGVTQEYIQTT IQKVTVDCKQYVCNGFQKCEQLLREYGQFCSKINqALHGANL RQDDSVRNLFASVKSSQSSPIIPGFGGDFNLTLLEPVSISTG SRSARSAIEDLLFDKVTIADPGYMQGYDDCMQQGPASARDLI CAQYVAGYKVLPPLMDVNMEAAYTSSLLGSIAGVGWTAGLSS FAAIPFAQSIFYRLNGVGITQQVLSENQKLIANKFNQALGAM QTGFTTTNEAFrKVQDAVNNNAQALSKLASELSNTFGAISAS IGDIIQRLDVLEQDAQIDRLINGRLTTLNAFVAQQLVRSESA ALSAQLAKDKVNECVKAQSKRSGFCGQGTHIVSFVVNAPNGL YFMHVGYYPSNHIEVVSAYGLCDAANPTNCIAPVNGYFIKTN NTRIVDEWSYTGSSFYAPEPITSLNTKYVAPQVTYQNISTNL PPPLLGNSTGIDFQDELDEFFKNVSTSIPNFGSLTQINTTLL DLTYEMLSLQQVVKALNESYIDLKELGNYTYYNKWPWYIWLG FIAGLVALALCVFFILCCTGCGTNCMGKLKCNRCCDRYEEYD LEPHKVHVH	24

TABLE 11-continued

Betacoronavirus Amino Acid Sequences

Strain	Amino Acid Sequence	SEQ ID NO:
MERS S FL SPIKE 2cEMC/2012 (XBaI change (T to G)) (amino acid)	MIHSVFLLMFLLTPTESYVDVGPDSVKSACIEVDIQQTFFDK TWPRPIDVSKADGIIYPQGRTYSNITITYQGLFPYQGDHGDM YVYSAGHATGTTPQKLFVANYSQDVKQFANGFVVRIGAAANS TGTVIISPSTSATIRKIYPAFMLGSSVGNFSDGKMGRFFNHT LVLLPDGCGTLLRAFYCILEPRSGNHCPAGNSYTSFATYHTP ATDCSDGNYNRNASLNSFKEYFNLRNCTFMYTYNITEDEILE WFGITQTAQGVHLFSSRYVDLYGGNMFQFATLPVYDTIKYYS IIPHSIRSIQSDRKAWAAFYVYKLQPLTFLLDFSVDGYIRRA IDCGFNDLSQLHCSYESFDVESGVYSVSSFEAKPSGSVVEQA EGVECDFSPLLSGTPPQVYNFKRLVFTNCNYNLTKLLSLFSV NDFTCSQISPAAIASNCYSSLILDYFSYPLSMKSDLSVSSAG PISQFNYKQSFSNPTCLILATVPHNLTTITKPLKYSYINKCS RLLSDDRTEVPQLVNANQYSPCVSIVPSTVWEDGDYYRKQLS PLEGGGWLVASGSTVAMTEQLQMGFGITVQYGTDTNSVCPKL EFANDTKIASQLGNCVEYSLYGVSGRGVFQNCTAVGVRQQRF VYDAYQNLVGYYSDDGNYYCLRACVSVPVSVIYDKETKTHAT LFGSVACEHISSTMSQYSRSTRSMLKRRDSTYGPLQTPVGCV LGLVNSSLFVEDCKLPLGQSLCALPDTPSTLTPRSVRSVPGE MRLASIAFNHPIQVDQLNSSYFKLSIPTNFSFGVTQEYIQTT IQKVTVDCKQYVCNGFQKCEQLLREYGQFCSKINQALHGANL RQDDSVRNLFASVKSSQSSPIIPGFGGDFNLTLLEPVSISTG SRSARSAIEDLLFDKVTIADPGYMQGYDDCMQQGPASARDLI CAQYVAGYKVLPPLMDVNMEAAYTSSLLGSIAGVGWTAGLSS FAAIPFAQSIFYRLNGVGITQQVLSENQKLIANKFNQALGAM QTGFTTTNEAFQKVQDAVNNNAQALSKLASELSNTFGAISAS IGDIIQRLDVLEQDAQIDRLINGRLTTLNAFVAQQLVRSESA ALSAQLAKDKVNECVKAQSKRSGFCGQGTHIVSFVVNAPNGL YFMHVGYYPSNHIEVVSAYGLCDAANPTNCIAPVNGYFIKTN NTRIVDEWSYTGSSFYAPEPITSLNTKYVAPQVTYQNISTNL PPPLLGNSTGIDFQDELDEFFKNVSTSIPNFGSLTQINTTLL DLTYEMLSLQQVVKALNESYIDLKELGNYTYYNKWPWYIWLG FIAGLVALALCVFFILCCTGCGTNCMGKLKCNRCCDRYEEYD LEPHKVHVH	25
Novel_MERS_S2_sub-unit_trimeric vaccine (amino acid)	MIHSVFLLMFLLTPTESDCKLPLGQSLCALPDTPSTLTPRSV RSVPGEMRLASIAFNHPIQVDQLNSSYFKLSIPTNFSFGVTQ EYIQTTIQKVTVDCKQYVCNGFQKCEQLLREYGQFCSKINQA LHGANLRQDDSVRNLFASVKSSQSSPIIPGFGGDFNLTLLEP VSISTGSRSARSAIEDLLFDKVTIADPGYMQGYDDCMQQGPA SARDLICAQYVAGYKVLPPLMDVNMEAAYTSSLLGSIAGVGW TAGLSSFAAIPFAQSIFYRLNGVGITQQVLSENQKLIANKFN QALGAMQTGFTTTNEAFQKVQDAVNNNAQALSKLASELSNTF GAISASIGDIIQRLDVLEQDAQIDRLINGRLTTLNAFVAQQL VRSESAALSAQLAKDKVNECVKAQSKRSGFCGQGTHIVSFVV NAPNGLYFMHVGYYPSNHIEVVSAYGLCDAANPTNCIAPVNG YFIKTNNTRIVDEWSYTGSSFYAPEPITSLNTKYVAPQVTYQ NISTNLPPPLLGNSTGIDFQDELDEFFKNVSTSIPNFGSLTQ INTTLLDLTYEMLSLQQVVKALNESYIDLKELGNYTYYNKWP DKIEEILSKIYHIENEIARIKKLIGEA	26
Isolate A1-Hasa_1_2013 (NCBI accession #AGN70962)	MIHSVFLLMFLLTPTESYVDVGPDSVKSACIEVDIQQTFFDK TWPRPIDVSKADGIIYPQGRTYSNITITYQGLFPYQGDHGDM YVYSAGHATGTTPQKLFVANYSQDVKQFANGFVVRIGAAANS TGTVIISPSTSATIRKIYPAFMLGSSVGNFSDGKMGRFFNHT LVLLPDGCGTLLRAFYCILEPRSGNHCPAGNSYTSFATYHTP ATDCSDGNYNRNASLNSFKEYFNLRNCTFMYTYNITEDEILE WFGITQTAQGVHLFSSRYVDLYGGNMFQFATLPVYDTIKYYS IIPHSIRSIQSDRKAWAAFYVYKLQPLTFLLDFSVDGYIRRA IDCGFNDLSQLHCSYESFDVESGVYSVSSFEAKPSGSVVEQA EGVECDFSPLLSGTPPQVYNFKRLVFTNCNYNLTKLLSLFSV NDFTCSQISPAAIASNCYSSLILDYFSYPLSMKSDLSVSSAG PISQFNYKQSFSNPTCLILATVPHNLTTITKPLKYSYINKCS RLLSDDRTEVPQLVNANQYSPCVSIVPSTVWEDGDYYRKQLS PLEGGGWLVASGSTVAMTEQLQMGFGITVQYGTDTNSVCPKL EFANDTKIASQLGNCVEYSLYGVSGRGVFQNCTAVGVRQQRF VYDAYQNLVGYYSDDGNYYCLRACVSVPVSVIYDKETKTHAT LFGSVACEHISSTMSQYSRSTRSMLKRRDSTYGPLQTPVGCV LGLVNSSLFVEDCKLPLGQSLCALPDTPSTLTPRSVRSVPGE MRLASIAFNHPIQVDQLNSSYFKLSIPTNFSFGVTQEYIQTT IQKVTVDCKQYVCNGFQKCEQLLREYGQFCSKINQALHGANL RQDDSVRNLFASVKSSQSSPIIPGFGGDFNLTLLEPVSISTG SRSARSAIEDLLFDKVTIADPGYMQGYDDCMQQGPASARDLI CAQYVAGYKVLPPLMDVNMEAAYTSSLLGSIAGVGWTAGLSS FAAIPFAQSIFYRLNGVGITQQVLSENQKLIANKFNQALGAM	27

TABLE 11-continued

Betacoronavirus Amino Acid Sequences

Strain	Amino Acid Sequence	SEQ ID NO:
	QTGFTTTNEAFRKVQDAVNNNAQALSKLASELSNTFGAISAS IGDIIQRLDVLEQDAQIDRLINGRLTTLNAFVAQQLVRSESA ALSAQLAKDKVNECVKAQSKRSGFCGQGTHIVSFVVNAPNGL YFMHVGYYPSNHIEVVSAYGLCDAANPTNCIAPVNGYFIKTN NTRIVDEWSYTGSSFYAPEPITSLNTKYVAPHVTYQNISTNL PPPLLGNSTGIDFQDELDEFFKNVSTSIPNFGSLTQINTTLL DLTYEMLSLQQVVKALNESYIDLKELGNYTYYNKWPWYIWLG FIAGLVALALCVFFILCCTGCGTNCMGKLKCNRCCDRYEEYD LEPHKVHVH	
Middle East respiratory syndrome coronavirus S protein UniProtKB-R9UQ53	MIHSVFLLMFLLTPTESYVDVGPDSVKSACIEVDIQQTFFDK TWPRPIDVSKADGIIYPQGRTYSNITITYQGLFPYQGDHGDM YVYSAGHATGTTPQKLFVANYSQDVKQFANGFVVRIGAAANS TGTVIISPSTSATIRKIYPAFMLGSSVGNFSDGKMGRFFNHT LVLLPDGCGTLLRAFYCILEPRSGNHCPAGNSYTSFATYHTP ATDCSDGNYNRNASLNSFKEYFNLRNCTFMYTYNITEDEILE WFGITQTAQGVHLFSSRYVDLYGGNMFQFATLPVYDTIKYYS IIPHSIRSIQSDRKAWAAFYVYKLQPLTFLLDFSVDGYIRRA IDCGFNDLSQLHCSYESFDVESGVYSVSSFEAKPSGSVVEQA EGVECDFSPLLSGTPPQVYNFKRLVFTNCNYNLTKLLSLFSV NDFTCSQISPAAIASNCYSSLILDYFSYPLSMKSDLSVSSAG PISQFNYKQSFSNPTCLILATVPHNLTTITKPLKYSYINKCS RLLSDDRTEVPQLVNANQYSPCVSIVPSTVWEDGDYYRKQLS PLEGGGWLVASGSTVAMTEQLQMGFGITVQYGTDTNSVCPKL EFANDTKIASQLGNCVEYSLYGVSGRGVFQNCTAVGVRQQRF VYDAYQNLVGYYSDDGNYYCLRACVSVPVSVIYDKETKTHAT LFGSVACEHISSTMSQYSRSTRSMLKRRDSTYGPLQTPVGCV LGLVNSSLFVEDCKLPLGQSLCALPDTPSTLTPRSVRSVPGE MRLASIAFNHPIQVDQLNSSYFKLSIPTNFSFGVTQEYIQTT IQKVTVDCKQYVCNGFQKCEQLLREYGQFCSKINQALHGANL RQDDSVRNLFASVKSSQSSPIIPGFGGDFNLTLLEPVSISTG SRSARSAIEDLLFDKVTIADPGYMQGYDDCMQQGPASARDLI CAQYVAGYKVLPPLMDVNMEAAYTSSLLGSIAGVGWTAGLSS FAAIPFAQSIFYRLNGVGITQQVLSENQKLIANKFNQALGAM QTGFTTTNEAFRKVQDAVNNNAQALSKLASELSNTFGAISAS IGDIIQRLDVLEQDAQIDRLINGRLTTLNAFVAQQLVRSESA ALSAQLAKDKVNECVKAQSKRSGFCGQGTHIVSFVVNAPNGL YFMHVGYYPSNHIEVVSAYGLCDAANPTNCIAPVNGYFIKTN NTRIVDEWSYTGSSFYAPEPITSLNTKYVAPHVTYQNISTNL PPPLLGNSTGIDFQDELDEFFKNVSTSIPNFGSLTQINTTLL DLTYEMLSLQQVVKALNESYIDLKELGNYTYYNKWPWYIWLG FIAGLVALALCVFFILCCTGCGTNCMGKLKCNRCCDRYEEYD LEPHKVHVH	28
Human SARS coronavirus (SARS-CoV) (Severe acute respiratory syndrome coronavirus) Spike glycoprotein UniProtKB-P59594	MFIFLLFLTLTSGSDLDRCTTFDDVQAPNYTQHTSSMRGVYY PDEIFRSDTLYLTQDLFLPFYSNVTGFHTINHTFGNPVIPFK DGIYFAATEKSNVVRGWVFGSTMNNKSQSVIIINNSTNVVIR ACNFELCDNPFFAVSKPMGTQTHTMIFDNAFNCTFEYISDAF SLDVSEKSGNFKHLREFVFKNKDGFLYVYKGYQPIDVVRDLP SGFNTLKPIFKLPLGINITNFRAILTAFSPAQDIWGTSAAAY FVGYLKPTTFMLKYDENGTITDAVDCSQNPLAELKCSVKSFE IDKGIYQTSNFRVVPSGDVVRFPNITNLCPFGEVFNATKFPS VYAWERKKISNCVADYSVLYNSTFFSTFKCYGVSATKLNDLC FSNVYADSFVVKGDDVRQIAPGQTGVIADYNYKLPDDFMGCV LAWNTRNIDATSTGNYNYKYRYLRHGKLRPFERDISNVPFSP DGKPCTPPALNCYWPLNDYGFYTTTGIGYQPYRVVVLSFELL NAPATVCGPKLSTDLIKNQCVNFNFNGLTGTGVLTPSSKRFQ PFQQFGRDVSDFTDSVRDPKTSEILDISPCSFGGVSVITPGT NASSEVAVLYQDVNCTDVSTAIHADQLTPAWRIYSTGNNVFQ TQAGCLIGAEHVDTSYECDIPIGAGICASYHTVSLLRSTSQK SIVAYTMSLGADSSIAYSNNTIAIPTNFSISITTEVMPVSMA KTSVDCNMYICGDSTECANLLLQYGSFCTQLNRALSGIAAEQ DRNTREVFAQVKQMYKTPTLKYFGGFNFSQILPDPLKPTKRS FIEDLLFNKVTLADAGFMKQYGECLGDINARDLICAQKFNGL TVLPPLLTDDMIAAYTAALVSGTATAGWTFGAGAALQIPFAM QMAYRFNGIGVTQNVLYENQKQIANQFNKAISQIQESLTTTS TALGKLQDVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRL DKVEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAA TKMSECVLGQSKRVDFCGKGYHLMSFPQAAPHGVVFLHVTYV PSQERNFTTAPAICHEGKAYFPREGVFVFNGTSWFITQRNFF SPQIITTDNTFVSGNCDVVIGIINNTVYDPLQPELDSFKEEL DKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLN ESLIDLQELGKYEQYIKWPWYVWLGFIAGLIAIVMVTILLCC MTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT	29

TABLE 11-continued

Betacoronavirus Amino Acid Sequences

Strain	Amino Acid Sequence	SEQ ID NO:
Human coronavirus OC43 (HCoV-OC43) Spike glycoprotein UniProtKB-P36334	MFLILLISLPTAFAVIGDLKCTSDNINDKDTGPPPISTDTVD VTNGLGTYYVLDRVYLNTTLFLNGYYPTSGSTYRNMALKGSV LLSRLWFKPPFLSDFINGIFAKVKNTKVIKDRVMYSEFPAIT IGSTFVNTSYSVVVQPRTINSTQDGDNKLQGLLEVSVCQYNM CEYPQTICHPNLGNHRKELWHLDTGVVSCLYKRNFTYDVNAD YLYFHFYQEGGTFYAYFTDTGVVTKFLFNVYLGMALSHYYVM PLTCNSKLTLEYWVTPLTSRQYLLAFNQDGIIFNAEDCMSDF MSEIKCKTQSIAPPTGVYELNGYTVQPIADVYRRKPNLPNCN IEAWLNDKSVPSPLNWERKTFSNCNFNMSSLMSFIQADSFTC NNIDAAKIYGMCFSSITIDKFAIPNGRKVDLQLGNLGYLQSF NYRIDTTATSCQLYYNLPAANVSVSRFNPSTWNKRFGFIEDS VFKPRPAGVLTNHDVVYAQHCFKAPKNFCPCKLNGSCVGSGP GKNNGIGTCPAGTNYLTCDNLCTPDPITFTGTYKCPQTKSLV GIGEHCSGLAVKSDYCGGNSCTCRPQAFLGWSADSCLQGDKC NIFANFILHDVNSGLTCSTDLQKANTDIILGVCVNYDLYGIL GQGIFVEVNATYYNSWQNLLYDSNGNLYGFRDYIINRTFMIR SCYSGRVSAAFHANSSEPALLFRNIKCNYVFNNSLTRQLQPI NYFDSYLGCVVNAYNSTAISVQTCDLTVGSGYCVDYSKNRRS RGAITTGYRFTNFEPFTVNSVNDSLEPVGGLYEIQIPSEFTI GNMVEFIQTSSPKVTIDCAAFVCGDYAACKSQLVEYGSFCDN INAILTEVNELLDTTQLQVANSLMNGVTLSTKLKDGVNFNVD DINFSPVLGCLGSECSKASSRSAIEDLLFDKVKLSDVGFVEA YNNCTGGAEIRDLICVQSYKGIKVLPPLLSENQISGYTLAAT SASLFPPWTAAAGVPFYLNVQYRINGLGVTMDVLSQNQKLIA NAFNNALYAIQEGFDATNSALVKIQAVVNANAEALNNLLQQL SNRFGAISASLQEILSRLDALEAEAQIDRLINGRLTALNAYV SQQLSDSTLVKFSAAQAMEKVNECVKSQSSRINFCGNGNHII SLVQNAPYGLYFIHFSYVPTKYVTARVSPGLCIAGDRGIAPK SGYFVNVNNTWMYTGSGYYYPEPITENNVVVMSTCAVNYTKA PYVMLNTSIPNLPDFKEELDQWFKNQTSVAPDLSLDYINVTF LDLQVEMNRLQEAIKVLNQSYINLKDIGTYEYYVKWPWYVWL LICLAGVAMLVLLFFICCCTGCGTSCFKKCGGCCDDYTGYQE LVIKTSHDD	30
Human coronavirus HKU1 (isolate N5) (HCoV-HKU1) Spike glycoprotein UniProtKB-Q0ZME7	MFLIIFILPTTLAVIGDFNCTNSFINDYNKTIPRISEDVVDV SLGLGTYYVLNRVYLNTTLLFTGYFPKSGANFRDLALKGSIY LSTLWYKPPFLSDFNNGIFSKVKNTKLYVNNTLYSEFSTIVI GSVFVNTSYTIVVQPHNGILEITACQYTMCEYPHTVCKSKGS IRNESWHIDSSEPLCLFKKNFTYNVSADWLYFHFYQERGVFY AYYADVGMPTTFLFSLYLGTILSHYYVMPLTCNAISSNTDNE TLEYWVTPLSRRQYLLNFDEHGVITNAVDCSSSFLSEIQCKT QSFAPNTGVYDLSGFTVKPVATVYRRIPNLPDCDIDNWLNNV SVPSPLNWERRIFSNCNFNLSTLLRLVHVDSFSCNNLDKSKI FGSCFNSITVDKFAIPNRRRDDLQLGSSGFLQSSNYKIDISS SSCQLYYSLPLVNVTINNFNPSSWNRRYGFGSFNLSSYDVVY SDHCFSVNSDFCPCADPSVVNSCAKSKPPSAICPAGTKYRHC DLDTTLYVKNWCRCSCLPDPISTYSPNTCPQKKVVVGIGEHC PGLGINEEKCGTQLNHSSCFCSPDAFLGWSFDSCISNNRCNI FSNFIFNGINSGTTCSNDLLYSNTEISTGVCVNYDLYGITGQ GIFKEVSAAYYNNWQNLLYDSNGNIIGFKDFLTNKTYTILPC YSGRVSAAFYQNSSSPALLYRNLKCSYVLNNISFISQPFYFD SYLGCVLNAVNLTSYSVSSCDLRMGSGFCIDYALPSSRRKRR GISSPYRFVTFEPFNVSFVNDSVETVGGLFEIQIPTNFTIAG HEEFIQTSSPKVTIDCSAFVCSNYAACHDLLSEYGTFCDNIN SILNEVNDLLDITQLQVANALMQGVTLSSNLNTNLHSDVDNI DFKSLLGCLGSQCGSSSRSLLEDLLFNKVKLSDVGFVEAYNN CTGGSEIRDLLCVQSFNGIKVLPPILSETQISGYTTAATVAA MFPPWSAAAGVPFSLNVQYRINGLGVTMDVLNKNQKLIANAF NKALLSIQNGFTATNSALAKIQSVVNANAQALNSLLQQLFNK FGAISSSLQEILSRLDNLEAQVQIDRLINGRLTALNAYVSQQ LSDITLIKAGASRAIEKVNECVKSQSPRINFCGNGNHILSLV QNAPYGLLFIHFSYKPTSFKTVLVSPGLCLSGDRGIAPKQGY FIKQNDSWMFTGSSYYYPEPISDKNVVFMNSCSVNFTKAPFI YLNNSIPNLSDFEAELSLWFKNHTSIAPNLTFNSHINATFLD LYYEMNVIQESIKSLNSSFINLKEIGTYEMYVKWPWYIWLLI VILFIIFLMILFFICCCTGCGSACFSKCHNCCDEYGGHNDFV IKASHDD	31
Novel_SARS_S2	MFIFLLFLTLTSGSDLDRALSGIAAEQDRNTREVFAQVKQMY KTPTLKYFGGFNFSQILPDPLKPTKRSFIEDLLFNKVTLADA GFMKQYGECLGDINARDLICAQKFNGLTVLPPLLTDDMIAAY TAALVSGTATAGWTFGAGAALQIPFAMQMAYRFNGIGVTQNV LYENQKQIANQFNKAISQIQESLTTTSTALGKLQDVVNQNAQ ALNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITG RLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVD	32

TABLE 11-continued

Betacoronavirus Amino Acid Sequences

Strain	Amino Acid Sequence	SEQ ID NO:
	FCGKGYHLMSFPQAAPHGVVFLHVTYVPSQERNFTTAPAICH EGKAYFPREGVFVFNGTSWFITQRNFFSPQIITTDNTFVSGN CDVVIGIINNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLG DISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQY IKWPWYVWLGFIAGLIAIVMVTILLCCMTSCCSCLKGACSCG SCCKFDEDDSEPVLKGVKLHYT	
Novel_MERS_S2	MIHSVFLLMFLLTPTESDCKLPLGQSLCALPDTPSTLTPRSV RSVPGEMRLASIAFNHPIQVDQLNSSYFKLSIPTNFSFGVTQ EYIQTTIQKVTVDCKQYVCNGFQKCEQLLREYGQFCSKINQA LHGANLRQDDSVRNLFASVKSSQSSPIIPGFGGDFNLTLLEP VSISTGSRSARSAIEDLLFDKVTIADPGYMQGYDDCMQQGPA SARDLICAQYVAGYKVLPPLMDVNMEAAYTSSLLGSIAGVGW TAGLSSFAAIPFAQSIFYRLNGVGITQQVLSENQKLIANKFN QALGAMQTGFTTTNEAFQKVQDAVNNNAQALSKLASELSNTF GAISASIGDIIQRLDVLEQDAQIDRLINGRLTTLNAFVAQQL VRSESAALSAQLAKDKVNECVKAQSKRSGFCGQGTHIVSFVV NAPNGLYFMHVGYYPSNHIEVVSAYGLCDAANPTNCIAPVNG YFIKTNNTRIVDEWSYTGSSFYAPEPITSLNTKYVAPQVTYQ NISTNLPPPLLGNSTGIDFQDELDEFFKNVSTSIPNFGSLTQ INTTLLDLTYEMLSLQQVVKALNESYIDLKELGNYTYYNKWP	33
Novel_Trimeric_SARS_S2	MFIFLLFLTLTSGSDLDRALSGIAAEQDRNTREVFAQVKQMY KTPTLKYFGGFNFSQILPDPLKPTKRSFIEDLLFNKVTLADA GFMKQYGECLGDINARDLICAQKFNGLTVLPPLLTDDMIAAY TAALVSGTATAGWTFGAGAALQIPFAMQMAYRFNGIGVTQNV LYENQKQIANQFNKAISQIQESLTTTSTALGKLQDVVNQNAQ ALNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITG RLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVD FCGKGYHLMSFPQAAPHGVVFLHVTYVPSQERNFTTAPAICH EGKAYFPREGVFVFNGTSWFITQRNFFSPQIITTDNTFVSGN CDVVIGIINNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLG DISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQY IKWPWYVWLGFIAGLIAIVMVTILLCCMTSCCSCLKGACSCG SCCKFDEDDSEPVLKGVKLHYT	34

TABLE 12

Full-length Spike Glycoprotein Amino Acid Sequences (*Homo sapiens* strains)

GenBank Accession	Country	Collection Date	Release Date	Virus Name
AFY13307	United Kingdom	2012 Sep. 11	2012 Dec. 5	Betacoronavirus England 1, complete genome
AFS88936		2012 Jun. 13	2012 Sep. 27	Human betacoronavirus 2c EMC/2012, complete genome
AGG22542	United Kingdom	2012 Sep. 19	2013 Feb. 27	Human betacoronavirus 2c England-Qatar/2012, complete genome
AHY21469	Jordan	2012	2014 May 4	Human betacoronavirus 2c Jordan-N3/2012 isolate MG167, complete genome
AGH58717	Jordan	2012 April	2013 Mar. 25	Human betacoronavirus 2c Jordan-N3/2012, complete genome
AGV08444	Saudi Arabia	2013 May 7	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Al-Hasa_12_2013, complete genome
AGV08546	Saudi Arabia	2013 May 11	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Al-Hasa_15_2013, complete genome
AGV08535	Saudi Arabia	2013 May 12	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Al-Hasa_16_2013, complete genome
AGV08558	Saudi Arabia	2013 May 15	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Al-Hasa_17_2013, complete genome
AGV08573	Saudi Arabia	2013 May 23	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Al-Hasa_18_2013, complete genome
AGV08480	Saudi Arabia	2013 May 23	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Al-Hasa_19_2013, complete genome

TABLE 12-continued

Full-length Spike Glycoprotein Amino Acid Sequences (*Homo sapiens* strains)

GenBank Accession	Country	Collection Date	Release Date	Virus Name
AGN70962	Saudi Arabia	2013 May 9	2013 Jun. 10	Middle East respiratory syndrome coronavirus isolate Al-Hasa_1_2013, complete genome
AGV08492	Saudi Arabia	2013 May 30	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Al-Hasa_21_2013, complete genome
AHI48517	Saudi Arabia	2013 May 2	2014 Feb. 6	Middle East respiratory syndrome coronavirus isolate Al-Hasa_25_2013, complete genome
AGN70951	Saudi Arabia	2013 Apr. 21	2013 Jun. 10	Middle East respiratory syndrome coronavirus isolate Al-Hasa_2_2013, complete genome
AGN70973	Saudi Arabia	2013 Apr. 22	2013 Jun. 10	Middle East respiratory syndrome coronavirus isolate Al-Hasa_3_2013, complete genome
AGN70929	Saudi Arabia	2013 May 1	2013 Jun. 10	Middle East respiratory syndrome coronavirus isolate Al-Hasa_4_2013, complete genome
AGV08408	Saudi Arabia	2012 Jun. 19	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Bisha_1_2012, complete genome
AGV08467	Saudi Arabia	2013 May 13	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Buraidah_1_2013, complete genome
AID50418	United Kingdom	2013 Feb. 10	2014 Jun. 18	Middle East respiratory syndrome coronavirus isolate England/2/2013, complete genome
AJD81451	United Kingdom	2013 Feb. 10	2015 Jan. 18	Middle East respiratory syndrome coronavirus isolate England/3/2013, complete genome
AJD81440	United Kingdom	2013 Feb. 13	2015 Jan. 18	Middle East respiratory syndrome coronavirus isolate England/4/2013, complete genome
AHB33326	France	2013 May 7	2013 Dec. 7	Middle East respiratory syndrome coronavirus isolate FRA/UAE, complete genome
AIZ48760	USA	2014 June	2014 Dec. 14	Middle East respiratory syndrome coronavirus isolate Florida/USA-2_Saudi Arabia_2014, complete genome
AGV08455	Saudi Arabia	2013 Jun. 4	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Hafr-Al-Batin_1_2013, complete genome
AHI48561	Saudi Arabia	2013 Aug. 5	2014 Feb. 6	Middle East respiratory syndrome coronavirus isolate Hafr-Al-Batin_2_2013, complete genome
AHI48539	Saudi Arabia	2013 Aug. 28	2014 Feb. 6	Middle East respiratory syndrome coronavirus isolate Hafr-Al-Batin_6_2013, complete genome
AIZ74417	France	2013 Apr. 26	2015 Mar. 10	Middle East respiratory syndrome coronavirus isolate Hu-France (UAE) - FRA1_1627-2013_BAL_Sanger, complete genome
AIZ74433	France	2013 May 7	2015 Mar. 10	Middle East respiratory syndrome coronavirus isolate Hu-France - FRA2_130569-2013_IS_HTS, complete genome
AIZ74439	France	2013 May 7	2015 Mar. 10	Middle East respiratory syndrome coronavirus isolate Hu-France - FRA2_130569-2013_InSpu_Sanger, complete genome
AIZ74450	France	2013 May 7	2015 Mar. 10	Middle East respiratory syndrome coronavirus isolate Hu-France - FRA2_130569-2013_Isolate_Sanger, complete genome
AKK52602	Saudi Arabia	2015 Feb. 10	2015 Jun. 8	Middle East respiratory syndrome coronavirus isolate Hu/Riyadh_KSA_2959_2015, complete genome
AKK52612	Saudi Arabia	2015 Mar. 1	2015 Jun. 8	Middle East respiratory syndrome coronavirus isolate Hu/Riyadh_KSA_4050_2015, complete genome

TABLE 12-continued

Full-length Spike Glycoprotein Amino Acid Sequences (*Homo sapiens* strains)

GenBank Accession	Country	Collection Date	Release Date	Virus Name
AHN10812	Saudi Arabia	2013 Nov. 6	2014 Mar. 24	Middle East respiratory syndrome coronavirus isolate Jeddah_1_2013, complete genome
AID55071	Saudi Arabia	2014 Apr. 21	2014 Nov. 12	Middle East respiratory syndrome coronavirus isolate Jeddah_C10306/KSA/2014-04-20, complete genome
AID55066	Saudi Arabia	2014	2014 Nov. 12	Middle East respiratory syndrome coronavirus isolate Jeddah_C7149/KSA/2014-04-05, complete genome
AID55067	Saudi Arabia	2014	2014 Nov. 12	Middle East respiratory syndrome coronavirus isolate Jeddah_C7569/KSA/2014-04-03, complete genome
AID55068	Saudi Arabia	2014 Apr. 7	2014 Nov. 12	Middle East respiratory syndrome coronavirus isolate Jeddah_C7770/KSA/2014-04-07, complete genome
AID55069	Saudi Arabia	2014 Apr. 12	2014 Nov. 12	Middle East respiratory syndrome coronavirus isolate Jeddah_C8826/KSA/2014-04-12, complete genome
AID55070	Saudi Arabia	2014 Apr. 14	2014 Nov. 12	Middle East respiratory syndrome coronavirus isolate Jeddah_C9055/KSA/2014-04-14, complete genome
AHE78108	Saudi Arabia	2013 Nov. 5	2014 May 1	Middle East respiratory syndrome coronavirus isolate MERS-CoV-Jeddah-human-1, complete genome
AKL59401	South Korea	2015 May 20	2015 Jun. 9	Middle East respiratory syndrome coronavirus isolate MERS-CoV/KOR/KNIH/002_05_2015, complete genome
ALD51904	Thailand	2015 Jun. 17	2015 Jul. 7	Middle East respiratory syndrome coronavirus isolate MERS-CoV/THA/CU/17_06_2015, complete genome
AID55072	Saudi Arabia	2014 Apr. 15	2014 Nov. 12	Middle East respiratory syndrome coronavirus isolate Makkah_C9355/KSA/Makkah/2014-04-15, complete genome
AHC74088	Qatar	2013 Oct. 13	2013 Dec. 23	Middle East respiratory syndrome coronavirus isolate Qatar3, complete genome
AHC74098	Qatar	2013 Oct. 17	2013 Dec. 23	Middle East respiratory syndrome coronavirus isolate Qatar4, complete genome
AHI48572	Saudi Arabia	2013 Aug. 15	2014 Feb. 6	Middle East respiratory syndrome coronavirus isolate Riyadh_14_2013, complete genome
AGV08379	Saudi Arabia	2012 Oct. 23	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Riyadh_1_2012, complete genome
AID55073	Saudi Arabia	2014 Apr. 22	2014 Nov. 12	Middle East respiratory syndrome coronavirus isolate Riyadh_2014KSA_683/KSA/2014, complete genome
AGV08584	Saudi Arabia	2012 Oct. 30	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Riyadh_2_2012, complete genome
AGV08390	Saudi Arabia	2013 Feb. 5	2013 Sep. 17	Middle East respiratory syndrome coronavirus isolate Riyadh_3_2013, complete genome
AHI48605	Saudi Arabia	2013 Mar. 1	2014 Feb. 6	Middle East respiratory syndrome coronavirus isolate Riyadh_4_2013, complete genome
AHI48583	Saudi Arabia	2013 Jul. 2	2014 Feb. 6	Middle East respiratory syndrome coronavirus isolate Riyadh_5_2013, complete genome
AHI48528	Saudi Arabia	2013 Jul. 17	2014 Feb. 6	Middle East respiratory syndrome coronavirus isolate Riyadh_9_2013, complete genome

TABLE 12-continued

Full-length Spike Glycoprotein Amino Acid Sequences (*Homo sapiens* strains)

GenBank Accession	Country	Collection Date	Release Date	Virus Name
AHI48594	Saudi Arabia	2013 Jun. 12	2014 Feb. 6	Middle East respiratory syndrome coronavirus isolate Taif_1_2013, complete genome
AHI48550	Saudi Arabia	2013 Jun. 12	2014 Feb. 6	Middle East respiratory syndrome coronavirus isolate Wadi-Ad-Dawasir_1_2013, complete genome
AIY60558	United Arab Emirates	2014 Mar. 7	2014 Dec. 6	Middle East respiratory syndrome coronavirus strain Abu Dhabi/Gayathi_UAE_2_2014, complete genome
AIY60538	United Arab Emirates	2014 Apr. 10	2014 Dec. 6	Middle East respiratory syndrome coronavirus strain Abu Dhabi_UAE_16_2014, complete genome
AIY60528	United Arab Emirates	2014 Apr. 10	2014 Dec. 6	Middle East respiratory syndrome coronavirus strain Abu Dhabi_UAE_18_2014, complete genome
AIY60588	United Arab Emirates	2014 Apr. 13	2014 Dec. 6	Middle East respiratory syndrome coronavirus strain Abu Dhabi_UAE_26_2014, complete genome
AIY60548	United Arab Emirates	2014 Apr. 19	2014 Dec. 6	Middle East respiratory syndrome coronavirus strain Abu Dhabi_UAE_30_2014, complete genome
AIY60568	United Arab Emirates	2014 Apr. 17	2014 Dec. 6	Middle East respiratory syndrome coronavirus strain Abu Dhabi_UAE_33_2014, complete genome
AIY60518	United Arab Emirates	2014 Apr. 7	2014 Dec. 6	Middle East respiratory syndrome coronavirus strain Abu Dhabi_UAE_8_2014, complete genome
AIY60578	United Arab Emirates	2013 Nov. 15	2014 Dec. 6	Middle East respiratory syndrome coronavirus strain Abu Dhabi_UAE_9_2013, complete genome
AKJ80137	China	2015 May 27	2015 Jun. 5	Middle East respiratory syndrome coronavirus strain ChinaGD01, complete genome
AHZ64057	USA	2014 May 10	2014 May 14	Middle East respiratory syndrome coronavirus strain Florida/USA-2_Saudi Arabia_2014, complete genome
AKM76229	Oman	2013 Oct. 28	2015 Jun. 23	Middle East respiratory syndrome coronavirus strain Hu/Oman_2285_2013, complete genome
AKM76239	Oman	2013 Dec. 28	2015 Jun. 23	Middle East respiratory syndrome coronavirus strain Hu/Oman_2874_2013, complete genome
AKI29284	Saudi Arabia	2015 Jan. 6	2015 May 27	Middle East respiratory syndrome coronavirus strain Hu/Riyadh-KSA-2049/2015, complete genome
AKI29265	Saudi Arabia	2015 Jan. 21	2015 May 27	Middle East respiratory syndrome coronavirus strain Hu/Riyadh-KSA-2343/2015, complete genome
AKI29255	Saudi Arabia	2015 Jan. 21	2015 May 27	Middle East respiratory syndrome coronavirus strain Hu/Riyadh-KSA-2345/2015, complete genome
AKI29275	Saudi Arabia	2015 Jan. 26	2015 May 27	Middle East respiratory syndrome coronavirus strain Hu/Riyadh-KSA-2466/2015, complete genome
AKK52582	Saudi Arabia	2015 Feb. 10	2015 Jun. 8	Middle East respiratory syndrome coronavirus strain Hu/Riyadh_KSA_2959_2015, complete genome
AKK52592	Saudi Arabia	2015 Mar. 1	2015 Jun. 8	Middle East respiratory syndrome coronavirus strain Hu/Riyadh_KSA_4050_2015, complete genome

TABLE 12-continued

Full-length Spike Glycoprotein Amino Acid Sequences (*Homo sapiens* strains)

GenBank Accession	Country	Collection Date	Release Date	Virus Name
AHZ58501	USA	2014 Apr. 30	2014 May 13	Middle East respiratory syndrome coronavirus strain Indiana/USA-1_Saudi Arabia_2014, complete genome
AGN52936	United Arab Emirates	2013	2013 Jun. 10	Middle East respiratory syndrome coronavirus, complete genome

TABLE 13

Description	Sequence	SEQ ID NO:
	MeV Nucleic Acid Sequences	
GC_F_MEASLES_B3.1 Sequence, NT (5' UTR, ORF, 3' UTR) Sequence Length: 1864	TCAAGCTTTTGGACCCTCGTACAGAAGCTAATACGACT CACTATAGGGAAATAAGAGAGAAAAGAAGAGTAAGAA GAAATATAAGAGCCACCATGGGTCTCAAGGTGAACGTC TCTGCCGTATTCATGGCAGTACTGTTAACTCTCCAAACA CCCGCCGGTCAAATTCATTGGGGCAATCTCTCTAAGAT AGGGGTAGTAGGAATAGGAAGTGCAAGCTACAAAGTT ATGACTCGTTCCAGCCATCAATCATTAGTCATAAAATT AATGCCCAATATAACTCTCCTCAATAACTGCACGAGGG TAGAGATTGCAGAATACAGGAGACTACTAAGAACAGTT TTGGAACCAATTAGGGATGCACTTAATGCAATGACCCA GAACATAAGGCCGGTTCAGAGCGTAGCTTCAAGTAGGA GACACAAGAGATTTGCGGGAGTAGTCCTGGCAGGTGCG GCCCTAGGTGTTGCCACAGCTGCTCAGATAACAGCCGG CATTGCACTTCACCGGTCCATGCTGAACTCTCAGGCCAT CGACAATCTGAGAGCGAGCCTGGAAACTACTAATCAGG CAATTGAGGCAATCAGACAAGCAGGGCAGGAGATGAT ATTGGCTGTTCAGGGTGTCCAAGACTACATCAATAATG AGCTGATACCGTCTATGAACCAGCTATCTTGTGATCTA ATCGGTCAGAAGCTCGGGCTCAAATTGCTTAGATACTA TACAGAAATCCTGTCATTATTTGGCCCCAGCCTACGGG ACCCCATATCTGCGGAGATATCTATCCAGGCTTTGAGTT ATGCACTTGGAGGAGATATCAATAAGGTGTTAGAAAAG CTCGGATACAGTGGAGGCGATTTACTAGGCATCTTAGA GAGCAGAGGAATAAAGGCTCGGATAACTCACGTCGAC ACAGAGTCCTACTTCATAGTCCTCAGTATAGCCTATCCG ACGCTGTCCGAGATTAAGGGGGTGATTGTCCACCGGCT AGAGGGGGTCTCGTACAACATAGGCTCTCAAGAGTGGT ATACCACTGTGCCCAAGTATGTTGCAACCCAAGGGTAC CTTATCTCGAATTTTGATGAGTCATCATGTACTTTCATG CCAGAGGGGACTGTGTGCAGCCAAAATGCCTTGTACCC GATGAGTCCTCTGCTCCAAGAATGCCTCCGGGGGTCCA CCAAGTCCTGTGCTCGTACACTCGTATCCGGGTCTTTTG GGAACCGGTTCATTTTATCACAAGGGAACCTAATAGCC AATTGTGCATCAATTCTTTGTAAGTGTTACACAACAGGT ACGATTATTAATCAAGACCCTGACAAGATCCTAACATA CATTGCTGCCGATCGCTGCCCGGTAGTCGAGGTGAACG GCGTGACCATCCAAGTCGGGAGCAGGAGGTATCCAGA CGCTGTGTACTTGCACAGAATTGACCTCGGTCCTCCCAT ATCATTGGAGAGGTTGGACGTAGGGACAAATCTGGGG AATGCAATTGCCAAATTGGAGGATGCCAAGGAATTGTT GGAATCATCGGACCAGATATTGAGAAGTATGAAAGGTT TATCGAGCACTAGCATAGTCTACATCCTGATTGCAGTG TGTCTTGGAGGGTTGATAGGGATCCCCACTTTAATATGT TGCTGCAGGGGGCGTTGTAACAAAAAGGGAGAACAAG TTGGTATGTCAAGACCAGGCCTAAAGCCTGACCTTACA GGAACATCAAAATCCTATGTAAGATCGCTTTGATGATA ATAGGCTGGAGCCTCGGTGGCCAAGCTTCTTGCCCCTT GGGCCTCCCCCCAGCCCCTCCTCCCCTTCCTGCACCCGT ACCCCCGTGGTCTTTGAATAAAGTCTGAGTGGGCGGC	35
GC_F_MEASLES_B3.1 ORF Sequence, NT	ATGGGTCTCAAGGTGAACGTCTCTGCCGTATTCATGGC AGTACTGTTAACTCTCCAAACACCCGCCGGTCAAATTC ATTGGGGCAATCTCTCTAAGATAGGGGTAGTAGGAATA GGAAGTGCAAGCTACAAAGTTATGACTCGTTCCAGCCA TCAATCATTAGTCATAAAATTAATGCCCAATATAACTCT CCTCAATAACTGCACGAGGGTAGAGATTGCAGAATACA GGAGACTACTAAGAACAGTTTTGGAACCAATTAGGGAT	36

TABLE 13-continued

Description	Sequence	SEQ ID NO:
	GCACTTAATGCAATGACCCAGAACATAAGGCCGGTTCA	
	GAGCGTAGCTTCAAGTAGGAGACACAAGAGATTTGCG	
	GGAGTAGTCCTGGCAGGTGCGGCCCTAGGTGTTGCCAC	
	AGCTGCTCAGATAACAGCCGGCATTGCACTTCACCGGT	
	CCATGCTGAACTCTCAGGCCATCGACAATCTGAGAGCG	
	AGCCTGGAAACTACTAATCAGGCAATTGAGGCAATCAG	
	ACAAGCAGGGCAGGAGATGATATTGGCTGTTCAGGGTG	
	TCCAAGACTACATCAATAATGAGCTGATACCGTCTATG	
	AACCAGCTATCTTGTGATCTAATCGGTCAGAAGCTCGG	
	GCTCAAATTGCTTAGATACTATACAGAAATCCTGTCATT	
	ATTTGGCCCCAGCCTACGGGACCCCATATCTGCGGAGA	
	TATCTATCCAGGCTTTGAGTTATGCACTTGGAGGAGAT	
	ATCAATAAGGTGTTAGAAAAGCTCGGATACAGTGGAG	
	GCGATTTACTAGGCATCTTAGAGAGCAGAGGAATAAAG	
	GCTCGGATAACTCACGTCGACACAGAGTCCTACTTCAT	
	AGTCCTCAGTATAGCCTATCCGACGCTGTCCGAGATTA	
	AGGGGGTGATTGTCCACCGGCTAGAGGGGGTCTCGTAC	
	AACATAGGCTCTCAAGAGTGGTATACCACTGTGCCCAA	
	GTATGTTGCAACCCAAGGGTACCTTATCTCGAATTTTGA	
	TGAGTCATCATGTACTTTCATGCCAGAGGGGACTGTGT	
	GCAGCCAAAATGCCTTGTACCCGATGAGTCCTCTGCTC	
	CAAGAATGCCTCCGGGGGTCCACCAAGTCCTGTGCTCG	
	TACACTCGTATCCGGGTCTTTTGGGAACCGGTTCATTTT	
	ATCACAAGGGAACCTAATAGCCAATTGTGCATCAATTC	
	TTTGTAAGTGTTACACAACAGGTACGATTATTAATCAA	
	GACCCTGACAAGATCCTAACATACATTGCTGCCGATCG	
	CTGCCCGGTAGTCGAGGTGAACGGCGTGACCATCCAAG	
	TCGGGAGCAGGAGGTATCCAGACGCTGTGTACTTGCAC	
	AGAATTGACCTCGGTCCTCCCATATCATTGGAGAGGTT	
	GGACGTAGGGACAAATCTGGGGAATGCAATTGCCAAA	
	TTGGAGGATGCCAAGGAATTGTTGGAATCATCGGACCA	
	GATATTGAGAAGTATGAAAGGTTTATCGAGCACTAGCA	
	TAGTCTACATCCTGATTGCAGTGTGTCTTGGAGGGTTGA	
	TAGGGATCCCCACTTTAATATGTTGCTGCAGGGGGCGT	
	TGTAACAAAAAGGGAGAACAAGTTGGTATGTCAAGAC	
	CAGGCCTAAAGCCTGACCTTACAGGAACATCAAAATCC	
	TATGTAAGATCGCTTTGA	
GC_F_MEASLES_B3.1 mRNA Sequence (assumes T100 tail) mRNA Sequence Length: 1925	G*GGGAAATAAGAGAGAAAAGAAGAGTAAGAAGAAAT	37
	ATAAGAGCCACCATGGGTCTCAAGGTGAACGTCTCTGC	
	CGTATTCATGGCAGTACTGTTAACTCTCCAAACACCCG	
	CCGGTCAAATTCATTGGGGCAATCTCTCTAAGATAGGG	
	GTAGTAGGAATAGGAAGTGCAAGCTACAAAGTTATGA	
	CTCGTTCCAGCCATCAATCATTAGTCATAAAATTAATGC	
	CCAATATAACTCTCCTCAATAACTGCACGAGGGTAGAG	
	ATTGCAGAATACAGGAGACTACTAAGAACAGTTTTGGA	
	ACCAATTAGGGATGCACTTAATGCAATGACCCAGAACA	
	TAAGGCCGGTTCAGAGCGTAGCTTCAAGTAGGAGACAC	
	AAGAGATTTGCGGGAGTAGTCCTGGCAGGTGCGGCCCT	
	AGGTGTTGCCACAGCTGCTCAGATAACAGCCGGCATTG	
	CACTTCACCGGTCCATGCTGAACTCTCAGGCCATCGAC	
	AATCTGAGAGCGAGCCTGGAAACTACTAATCAGGCAAT	
	TGAGGCAATCAGACAAGCAGGGCAGGAGATGATATTG	
	GCTGTTCAGGGTGTCCAAGACTACATCAATAATGAGCT	
	GATACCGTCTATGAACCAGCTATCTTGTGATCTAATCG	
	GTCAGAAGCTCGGGCTCAAATTGCTTAGATACTATACA	
	GAAATCCTGTCATTATTTGGCCCCAGCCTACGGGACCC	
	CATATCTGCGGAGATATCTATCCAGGCTTTGAGTTATGC	
	ACTTGGAGGAGATATCAATAAGGTGTTAGAAAAGCTCG	
	GATACAGTGGAGGCGATTTACTAGGCATCTTAGAGAGC	
	AGAGGAATAAAGGCTCGGATAACTCACGTCGACACAG	
	AGTCCTACTTCATAGTCCTCAGTATAGCCTATCCGACGC	
	TGTCCGAGATTAAGGGGGTGATTGTCCACCGGCTAGAG	
	GGGGTCTCGTACAACATAGGCTCTCAAGAGTGGTATAC	
	CACTGTGCCCAAGTATGTTGCAACCCAAGGGTACCTTA	
	TCTCGAATTTTGATGAGTCATCATGTACTTTCATGCCAG	
	AGGGGACTGTGTGCAGCCAAAATGCCTTGTACCCGATG	
	AGTCCTCTGCTCCAAGAATGCCTCCGGGGGTCCACCAA	
	GTCCTGTGCTCGTACACTCGTATCCGGGTCTTTTGGGAA	
	CCGGTTCATTTTATCACAAGGGAACCTAATAGCCAATT	
	GTGCATCAATTCTTTGTAAGTGTTACACAACAGGTACG	
	ATTATTAATCAAGACCCTGACAAGATCCTAACATACAT	
	TGCTGCCGATCGCTGCCCGGTAGTCGAGGTGAACGGCG	
	TGACCATCCAAGTCGGGAGCAGGAGGTATCCAGACGCT	
	GTGTACTTGCACAGAATTGACCTCGGTCCTCCCATATCA	
	TTGGAGAGGTTGGACGTAGGGACAAATCTGGGGAATG	
	CAATTGCCAAATTGGAGGATGCCAAGGAATTGTTGGAA	

TABLE 13-continued

Description	Sequence	SEQ ID NO:
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	GAGCACTAGCATAGTCTACATCCTGATTGCAGTGTGTC	
	TTGGAGGGTTGATAGGGATCCCCACTTTAATATGTTGCT	
	GCAGGGGGCGTTGTAACAAAAAGGGAGAACAAGTTGG	
	TATGTCAAGACCAGGCCTAAAGCCTGACCTTACAGGAA	
	CATCAAAATCCTATGTAAGATCGCTTTGATGATAATAG	
	GCTGGAGCCTCGGTGGCCAAGCTTCTTGCCCCTTGGGC	
	CTCCCCCCAGCCCCTCCTCCCCTTCCTGCACCCGTACCC	
	CCGTGGTCTTTGAATAAAGTCTGAGTGGGCGGCAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAATCTAG	
GC_F_MEASLES_D8 Sequence, NT (5' UTR, ORF, 3' UTR) Sequence Length: 1864	TCAAGCTTTTGGACCCTCGTACAGAAGCTAATACGACT	38
	CACTATAGGGAAATAAGAGAGAAAAGAAGAGTAAGAA	
	GAAATATAAGAGCCACCATGGGTCTCAAGGTGAACGTC	
	TCTGTCATATTCATGGCAGTACTGTTAACTCTTCAAACA	
	CCCACCGGTCAAATCCATTGGGGCAATCTCTCTAAGAT	
	AGGGGTGGTAGGGGTAGGAAGTGCAAGCTACAAAGTT	
	ATGACTCGTTCCAGCCATCAATCATTAGTCATAAAGTT	
	AATGCCCAATATAACTCTCCTCAACAATTGCACGAGGG	
	TAGGGATTGCAGAATACAGGAGACTACTGAGAACAGTT	
	CTGGAACCAATTAGAGATGCACTTAATGCAATGACCCA	
	GAATATAAGACCGGTTCAGAGTGTAGCTTCAAGTAGGA	
	GACACAAGAGATTTGCGGGAGTTGTCCTGGCAGGTGCG	
	GCCCTAGGCGTTGCCACAGCTGCTCAAATAACAGCCGG	
	TATTGCACTTCACCAGTCCATGCTGAACTCTCAAGCCAT	
	CGACAATCTGAGAGCGAGCCTAGAAACTACTAATCAGG	
	CAATTGAGGCAATCAGACAAGCAGGGCAGGAGATGAT	
	ATTGGCTGTTCAGGGTGTCCAAGACTACATCAATAATG	
	AGCTGATACCGTCTATGAATCAACTATCTTGTGATTTAA	
	TCGGCCAGAAGCTAGGGCTCAAATTGCTCAGATACTAT	
	ACAGAAATCCTGTCATTATTTGGCCCCAGCTTACGGGA	
	CCCCATATCTGCGGAGATATCTATCCAGGCTTTGAGCT	
	ATGCGCTTGGAGGAGATATCAATAAGGTGTTGGAAAAG	
	CTCGGATACAGTGGAGGTGATCTACTGGGCATCTTAGA	
	GAGCAGAGGAATAAAGGCCCGGATAACTCACGTCGAC	
	ACAGAGTCCTACTTCATTGTACTCAGTATAGCCTATCCG	
	ACGCTATCCGAGATTAAGGGGGTGATTGTCCACCGGCT	
	AGAGGGGGTCTCGTACAACATAGGCTCTCAAGAGTGGT	
	ATACCACTGTGCCCAAGTATGTTGCAACCCAAGGGTAC	
	CTTATCTCGAATTTTGATGAGTCATCATGCACTTTCATG	
	CCAGAGGGGACTGTGTGCAGCCAGAATGCCTTGTACCC	
	GATGAGTCCTCTGCTCCAAGAATGCCTCCGGGGGTCCA	
	CTAAGTCCTGTGCTCGTACACTCGTATCCGGGTCTTTCG	
	GGAACCGGTTCATTTTATCACAGGGGAACCTAATAGCC	
	AATTGTGCATCAATCCTTTGCAAGTGTTACACAACAGG	
	AACAATCATTAATCAAGACCCTGACAAGATCCTAACAT	
	ACATTGCTGCCGATCACTGCCCGGTGGTCGAGGTGAAT	
	GGCGTGACCATCCAAGTCGGGAGCAGGAGGTATCCGG	
	ACGCTGTGTACTTGCACAGGATTGACCTCGGTCCTCCC	
	ATATCTTTGGAGAGGTTGGACGTAGGGACAAATCTGGG	
	GAATGCAATTGCTAAGTTGGAGGATGCCAAGGAATTGT	
	TGGAGTCATCGGACCAGATATTGAGGAGTATGAAAGGT	
	TTATCGAGCACTAGTATAGTTTACATCCTGATTGCAGTG	
	TGTCTTGGAGGATTGATAGGGATCCCCGCTTTAATATGT	
	TGCTGCAGGGGGCGTTGTAACAAGAAGGGAGAACAAG	
	TTGGTATGTCAAGACCAGGCCTAAAGCCTGATCTTACA	
	GGAACATCAAAATCCTATGTAAGGTCACTCTGATGATA	
	ATAGGCTGGAGCCTCGGTGGCCAAGCTTCTTGCCCCTT	
	GGGCCTCCCCCCAGCCCCTCCTCCCCTTCCTGCACCCGT	
	ACCCCCGTGGTCTTTGAATAAAGTCTGAGTGGGCGGC	
GC_F_MEASLES_D8 ORF Sequence, NT	ATGGGTCTCAAGGTGAACGTCTCTGTCATATTCATGGC	39
	AGTACTGTTAACTCTTCAAACACCCACCGGTCAAATCC	
	ATTGGGGCAATCTCTCTAAGATAGGGGTGGTAGGGGTA	
	GGAAGTGCAAGCTACAAAGTTATGACTCGTTCCAGCCA	
	TCAATCATTAGTCATAAAGTTAATGCCCAATATAACTCT	
	CCTCAACAATTGCACGAGGGTAGGGATTGCAGAATACA	
	GGAGACTACTGAGAACAGTTCTGGAACCAATTAGAGAT	
	GCACTTAATGCAATGACCCAGAATATAAGACCGGTTCA	
	GAGTGTAGCTTCAAGTAGGAGACACAAGAGATTTGCGG	
	GAGTTGTCCTGGCAGGTGCGGCCCTAGGCGTTGCCACA	
	GCTGCTCAAATAACAGCCGGTATTGCACTTCACCAGTC	
	CATGCTGAACTCTCAAGCCATCGACAATCTGAGAGCGA	
	GCCTAGAAACTACTAATCAGGCAATTGAGGCAATCAGA	
	CAAGCAGGGCAGGAGATGATATTGGCTGTTCAGGGTGT	

TABLE 13-continued

Description	Sequence	SEQ ID NO:
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	ATCAACTATCTTGTGATTTAATCGGCCAGAAGCTAGGG	
	CTCAAATTGCTCAGATACTATACAGAAATCCTGTCATT	
	ATTTGGCCCCAGCTTACGGGACCCCATATCTGCGGAGA	
	TATCTATCCAGGCTTTGAGCTATGCGCTTGGAGGAGAT	
	ATCAATAAGGTGTTGGAAAAGCTCGGATACAGTGGAG	
	GTGATCTACTGGGCATCTTAGAGAGCAGAGGAATAAAG	
	GCCCGGATAACTCACGTCGACACAGAGTCCTACTTCAT	
	TGTACTCAGTATAGCCTATCCGACGCTATCCGAGATTA	
	AGGGGGTGATTGTCCACCGGCTAGAGGGGGTCTCGTAC	
	AACATAGGCTCTCAAGAGTGGTATACCACTGTGCCCAA	
	GTATGTTGCAACCCAAGGGTACCTTATCTCGAATTTTGA	
	TGAGTCATCATGCACTTTCATGCCAGAGGGGACTGTGT	
	GCAGCCAGAATGCCTTGTACCCGATGAGTCCTCTGCTC	
	CAAGAATGCCTCCGGGGGTCCACTAAGTCCTGTGCTCG	
	TACACTCGTATCCGGGTCTTTCGGGAACCGGTTCATTTT	
	ATCACAGGGGAACCTAATAGCCAATTGTGCATCAATCC	
	TTTGCAAGTGTTACACAACAGGAACAATCATTAATCAA	
	GACCCTGACAAGATCCTAACATACATTGCTGCCGATCA	
	CTGCCCGGTGGTCGAGGTGAATGGCGTGACCATCCAAG	
	TCGGGAGCAGGAGGTATCCGGACGCTGTGTACTTGCAC	
	AGGATTGACCTCGGTCCTCCCATATCTTTGGAGAGGTT	
	GGACGTAGGGACAAATCTGGGGAATGCAATTGCTAAGT	
	TGGAGGATGCCAAGGAATTGTTGGAGTCATCGGACCAG	
	ATATTGAGGAGTATGAAAGGTTTATCGAGCACTAGTAT	
	AGTTTACATCCTGATTGCAGTGTGTCTTGGAGGATTGAT	
	AGGGATCCCCGCTTTAATATGTTGCTGCAGGGGGCGTT	
	GTAACAAGAAGGGAGAACAAGTTGGTATGTCAAGACC	
	AGGCCTAAAGCCTGATCTTACAGGAACATCAAAATCCT	
	ATGTAAGGTCACTCTGA	
GC_F_MEASLES_D8	G*GGGAAATAAGAGAGAAAAGAAGAGTAAGAAGAAAT	40
mRNA Sequence	ATAAGAGCCACCATGGGTCTCAAGGTGAACGTCTCTGT	
(assumes T100 tail)	CATATTCATGGCAGTACTGTTAACTCTTCAAACACCCAC	
Sequence Length:	CGGTCAAATCCATTGGGGCAATCTCTCTAAGATAGGGG	
1925	TGGTAGGGGTAGGAAGTGCAAGCTACAAAGTTATGACT	
	CGTTCCAGCCATCAATCATTAGTCATAAAGTTAATGCC	
	CAATATAACTCTCCTCAACAATTGCACGAGGGTAGGGA	
	TTGCAGAATACAGGAGACTACTGAGAACAGTTCTGGAA	
	CCAATTAGAGATGCACTTAATGCAATGACCCAGAATAT	
	AAGACCGGTTCAGAGTGTAGCTTCAAGTAGGAGACACA	
	AGAGATTTGCGGGAGTTGTCCTGGCAGGTGCGGCCCTA	
	GGCGTTGCCACAGCTGCTCAAATAACAGCCGGTATTGC	
	ACTTCACCAGTCCATGCTGAACTCTCAAGCCATCGACA	
	ATCTGAGAGCGAGCCTAGAAACTACTAATCAGGCAATT	
	GAGGCAATCAGACAAGCAGGGCAGGAGATGATATTGG	
	CTGTTCAGGGTGTCCAAGACTACATCAATAATGAGCTG	
	ATACCGTCTATGAATCAACTATCTTGTGATTTAATCGGC	
	CAGAAGCTAGGGCTCAAATTGCTCAGATACTATACAGA	
	AATCCTGTCATTATTTGGCCCCAGCTTACGGGACCCCAT	
	ATCTGCGGAGATATCTATCCAGGCTTTGAGCTATGCGC	
	TTGGAGGAGATATCAATAAGGTGTTGGAAAAGCTCGGA	
	TACAGTGGAGGTGATCTACTGGGCATCTTAGAGAGCAG	
	AGGAATAAAGGCCCGGATAACTCACGTCGACACAGAG	
	TCCTACTTCATTGTACTCAGTATAGCCTATCCGACGCTA	
	TCCGAGATTAAGGGGGTGATTGTCCACCGGCTAGAGGG	
	GGTCTCGTACAACATAGGCTCTCAAGAGTGGTATACCA	
	CTGTGCCCAAGTATGTTGCAACCCAAGGGTACCTTATC	
	TCGAATTTTGATGAGTCATCATGCACTTTCATGCCAGAG	
	GGGACTGTGTGCAGCCAGAATGCCTTGTACCCGATGAG	
	TCCTCTGCTCCAAGAATGCCTCCGGGGGTCCACTAAGT	
	CCTGTGCTCGTACACTCGTATCCGGGTCTTTCGGGAACC	
	GGTTCATTTTATCACAGGGGAACCTAATAGCCAATTGT	
	GCATCAATCCTTTGCAAGTGTTACACAACAGGAACAAT	
	CATTAATCAAGACCCTGACAAGATCCTAACATACATTG	
	CTGCCGATCACTGCCCGGTGGTCGAGGTGAATGGCGTG	
	ACCATCCAAGTCGGGAGCAGGAGGTATCCGGACGCTGT	
	GTACTTGCACAGGATTGACCTCGGTCCTCCCATATCTTT	
	GGAGAGGTTGGACGTAGGGACAAATCTGGGGAATGCA	
	ATTGCTAAGTTGGAGGATGCCAAGGAATTGTTGGAGTC	
	ATCGGACCAGATATTGAGGAGTATGAAAGGTTTATCGA	
	GCACTAGTATAGTTTACATCCTGATTGCAGTGTGTCTTG	
	GAGGATTGATAGGGATCCCCGCTTTAATATGTTGCTGC	
	AGGGGGCGTTGTAACAAGAAGGGAGAACAAGTTGGTA	
	TGTCAAGACCAGGCCTAAAGCCTGATCTTACAGGAACA	
	TCAAAATCCTATGTAAGGTCACTCTGATGATAATAGGC	
	TGGAGCCTCGGTGGCCAAGCTTCTTGCCCCTTGGGCCTC	

TABLE 13-continued

Description	Sequence	SEQ ID NO:
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	TGGTCTTTGAATAAAGTCTGAGTGGGCGGCAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAATCTAG	
GC_H_MEASLES_B3 Sequence, NT (5' UTR, ORF, 3' UTR) Sequence Length: 2065	TCAAGCTTTTGGACCCTCGTACAGAAGCTAATACGACT	41
	CACTATAGGGAAATAAGAGAGAAAAGAAGAGTAAGAA	
	GAAATATAAGAGCCACCATGTCACCGCAACGAGACCG	
	GATAAATGCCTTCTACAAAGATAACCCTTATCCCAAGG	
	GAAGTAGGATAGTTATTAACAGAGAACATCTTATGATT	
	GACAGACCCTATGTTCTGCTGGCTGTTCTGTTCGTCATG	
	TTTCTGAGCTTGATCGGATTGCTGGCAATTGCAGGCATT	
	AGACTTCATCGGGCAGCCATCTACACCGCGGAGATCCA	
	TAAAAGCCTCAGTACCAATCTGGATGTGACTAACTCCA	
	TCGAGCATCAGGTCAAGGACGTGCTGACACCACTCTTT	
	AAAATCATCGGGGATGAAGTGGGCCTGAGAACACCTC	
	AGAGATTCACTGACCTAGTGAAATTCATCTCGGACAAG	
	ATTAAATTCCTTAATCCGGATAGGGAGTACGACTTCAG	
	AGATCTCACTTGGTGCATCAACCCGCCAGAGAGGATCA	
	AACTAGATTATGATCAATACTGTGCAGATGTGGCTGCT	
	GAAGAGCTCATGAATGCATTGGTGAACTCAACTCTACT	
	GGAGACCAGAACAACCACTCAGTTCCTAGCTGTCTCAA	
	AGGGAAACTGCTCAGGGCCCACTACAATCAGAGGTCA	
	ATTCTCAAACATGTCGCTGTCCTTGTTGGACTTGTACTT	
	AGGTCGAGGTTACAATGTGTCATCTATAGTCACTATGA	
	CATCCCAGGGAATGTATGGGGGAACCTACCTAGTTGAA	
	AAGCCTAATCTGAACAGCAAAGGGTCAGAGTTGTCACA	
	ACTGAGCATGTACCGAGTGTTTGAAGTAGGTGTGATCA	
	GAAACCCGGGTTTGGGGGCTCCGGTGTTCCATATGACA	
	AACTATTTTGAGCAACCAGTCAGTAATGGTCTCGGCAA	
	CTGTATGGTGGCTTTGGGGGAGCTCAAACTCGCAGCCC	
	TTTGTCACGGGGACGATTCTATCATAATTCCCTATCAGG	
	GATCAGGGAAAGGTGTCAGCTTCCAGCTCGTCAAGCTG	
	GGTGTCTGGAAATCCCCAACCGACATGCAATCCTGGGT	
	CCCCTTATCAACGGATGATCCAGTGGTAGACAGGCTTT	
	ACCTCTCATCTCACAGAGGTGTCATCGCTGACAATCAA	
	GCAAAATGGGCTGTCCCGACAACACGAACAGATGACA	
	AGTTGCGAATGGAGACATGCTTCCAGCAGGCGTGTAAA	
	GGTAAAATCCAAGCACTCTGCGAGAATCCCGAGTGGGT	
	ACCATTGAAGGATAACAGGATTCCTTCATACGGGGTCC	
	TGTCTGTTGATCTGAGTCTGACGGTTGAGCTTAAAATCA	
	AAATTGCTTCGGGATTCGGGCCATTGATCACACACGGC	
	TCAGGGATGGACCTATACAAATCCAACTGCAACAATGT	
	GTATTGGCTGACTATTCCGCCAATGAGAAATCTAGCCT	
	TAGGCGTAATCAACACATTGGAGTGGATACCGAGATTC	
	AAGGTTAGTCCCAACCTCTTCACTGTCCCAATTAAGGA	
	AGCAGGCGAAGACTGCCATGCCCCAACATACCTACCTG	
	CGGAGGTGGACGGTGATGTCAAACTCAGTTCCAACCTG	
	GTGATTCTACCTGGTCAAGATCTCCAATATGTTTTGGCA	
	ACCTACGATACCTCCAGGGTTGAGCATGCTGTGGTTTA	
	TTACGTTTACAGCCCAAGCCGCTCATTTTCTTACTTTTA	
	TCCTTTTAGGTTGCCTATAAAGGGGGTCCCAATCGAAC	
	TACAAGTGGAATGCTTCACATGGGATCAAAAACTCTGG	
	TGCCGTCACTTCTGTGTGCTTGCGGACTCAGAATCCGGT	
	GGACTTATCACTCACTCTGGGATGGTGGGCATGGGAGT	
	CAGCTGCACAGCTACCCGGGAAGATGGAACCAATCGC	
	AGATAATGATAATAGGCTGGAGCCTCGGTGGCCAAGCT	
	TCTTGCCCCTTGGGCCTCCCCCCAGCCCCTCCTCCCCTT	
	CCTGCACCCGTACCCCCGTGGTCTTTGAATAAAGTCTG	
	AGTGGGCGGC	
GC_H_MEASLES_B3 ORF Sequence, NT	ATGTCACCGCAACGAGACCGGATAAATGCCTTCTACAA	42
	AGATAACCCTTATCCCAAGGGAAGTAGGATAGTTATTA	
	ACAGAGAACATCTTATGATTGACAGACCCTATGTTCTG	
	CTGGCTGTTCTGTTCGTCATGTTTCTGAGCTTGATCGGA	
	TTGCTGGCAATTGCAGGCATTAGACTTCATCGGGCAGC	
	CATCTACACCGCGGAGATCCATAAAAGCCTCAGTACCA	
	ATCTGGATGTGACTAACTCCATCGAGCATCAGGTCAAG	
	GACGTGCTGACACCACTCTTTAAAATCATCGGGGATGA	
	AGTGGGCCTGAGAACACCTCAGAGATTCACTGACCTAG	
	TGAAATTCATCTCGGACAAGATTAAATTCCTTAATCCG	
	GATAGGGAGTACGACTTCAGAGATCTCACTTGGTGCAT	
	CAACCCGCCAGAGAGGATCAAACTAGATTATGATCAAT	
	ACTGTGCAGATGTGGCTGCTGAAGAGCTCATGAATGCA	
	TTGGTGAACTCAACTCTACTGGAGACCAGAACAACCAC	
	TCAGTTCCTAGCTGTCTCAAAGGGAAACTGCTCAGGGC	

TABLE 13-continued

Description	Sequence	SEQ ID NO:
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	TCCTTGTTGGACTTGTACTTAGGTCGAGGTTACAATGTG	
	TCATCTATAGTCACTATGACATCCCAGGGAATGTATGG	
	GGGAACCTACCTAGTTGAAAAGCCTAATCTGAACAGCA	
	AAGGGTCAGAGTTGTCACAACTGAGCATGTACCGAGTG	
	TTTGAAGTAGGTGTGATCAGAAACCCGGGTTTGGGGGC	
	TCCGGTGTTCCATATGACAAACTATTTTGAGCAACCAG	
	TCAGTAATGGTCTCGGCAACTGTATGGTGGCTTTGGGG	
	GAGCTCAAACTCGCAGCCCTTTGTCACGGGGACGATTC	
	TATCATAATTCCCTATCAGGGATCAGGGAAAGGTGTCA	
	GCTTCCAGCTCGTCAAGCTGGGTGTCTGGAAATCCCCA	
	ACCGACATGCAATCCTGGGTCCCCTTATCAACGGATGA	
	TCCAGTGGTAGACAGGCTTTACCTCTCATCTCACAGAG	
	GTGTCATCGCTGACAATCAAGCAAAATGGGCTGTCCCG	
	ACAACACGAACAGATGACAAGTTGCGAATGGAGACAT	
	GCTTCCAGCAGGCGTGTAAAGGTAAAATCCAAGCACTC	
	TGCGAGAATCCCGAGTGGGTACCATTGAAGGATAACAG	
	GATTCCTTCATACGGGGTCCTGTCTGTTGATCTGAGTCT	
	GACGGTTGAGCTTAAAATCAAAATTGCTTCGGGATTCG	
	GGCCATTGATCACACACGGCTCAGGGATGGACCTATAC	
	AAATCCAACTGCAACAATGTGTATTGGCTGACTATTCC	
	GCCAATGAGAAATCTAGCCTTAGGCGTAATCAACACAT	
	TGGAGTGGATACCGAGATTCAAGGTTAGTCCCAACCTC	
	TTCACTGTCCCAATTAAGGAAGCAGGCGAAGACTGCCA	
	TGCCCCAACATACCTACCTGCGGAGGTGGACGGTGATG	
	TCAAACTCAGTTCCAACCTGGTGATTCTACCTGGTCAA	
	GATCTCCAATATGTTTTGGCAACCTACGATACCTCCAG	
	GGTTGAGCATGCTGTGGTTTATTACGTTTACAGCCCAA	
	GCCGCTCATTTTCTTACTTTTATCCTTTTAGGTTGCCTAT	
	AAAGGGGGTCCCAATCGAACTACAAGTGGAATGCTTCA	
	CATGGGATCAAAAACTCTGGTGCCGTCACTTCTGTGTG	
	CTTGCGGACTCAGAATCCGGTGGACTTATCACTCACTCT	
	GGGATGGTGGGCATGGGAGTCAGCTGCACAGCTACCCG	
	GGAAGATGGAACCAATCGCAGATAA	
GC_H_MEASLES_B3 mRNA Sequence (assumes T100 tail) Sequence Length: 2126	G*GGGAAATAAGAGAGAAAAGAAGAGTAAGAAGAAAT ATAAGAGCCACCATGTCACCGCAACGAGACCGGATAA ATGCCTTCTACAAAGATAACCCTTATCCCAAGGGAAGT AGGATAGTTATTAACAGAGAACATCTTATGATTGACAG ACCCTATGTTCTGCTGGCTGTTCTGTTCGTCATGTTTCT GAGCTTGATCGGATTGCTGGCAATTGCAGGCATTAGAC TTCATCGGGCAGCCATCTACACCGCGGAGATCCATAAA AGCCTCAGTACCAATCTGGATGTGACTAACTCCATCGA GCATCAGGTCAAGGACGTGCTGACACCACTCTTTAAAA TCATCGGGGATGAAGTGGGCCTGAGAACACCTCAGAG ATTCACTGACCTAGTGAAATTCATCTCGGACAAGATTA AATTCCTTAATCCGGATAGGGAGTACGACTTCAGAGAT CTCACTTGGTGCATCAACCCGCCAGAGAGGATCAAACT AGATTATGATCAATACTGTGCAGATGTGGCTGCTGAAG AGCTCATGAATGCATTGGTGAACTCAACTCTACTGGAG ACCAGAACAACCACTCAGTTCCTAGCTGTCTCAAAGGG AAACTGCTCAGGGCCCACTACAATCAGAGGTCAATTCT CAAACATGTCGCTGTCCTTGTTGGACTTGTACTTAGGTC GAGGTTACAATGTGTCATCTATAGTCACTATGACATCC CAGGGAATGTATGGGGGAACCTACCTAGTTGAAAAGCC TAATCTGAACAGCAAAGGGTCAGAGTTGTCACAACTGA GCATGTACCGAGTGTTTGAAGTAGGTGTGATCAGAAAC CCGGGTTTGGGGGCTCCGGTGTTCCATATGACAAACTA TTTTGAGCAACCAGTCAGTAATGGTCTCGGCAACTGTA TGGTGGCTTTGGGGGAGCTCAAACTCGCAGCCCTTTGT CACGGGGACGATTCTATCATAATTCCCTATCAGGGATC AGGGAAAGGTGTCAGCTTCCAGCTCGTCAAGCTGGGTG TCTGGAAATCCCCAACCGACATGCAATCCTGGGTCCCC TTATCAACGGATGATCCAGTGGTAGACAGGCTTTACCT CTCATCTCACAGAGGTGTCATCGCTGACAATCAAGCAA AATGGGCTGTCCCGACAACACGAACAGATGACAAGTTG CGAATGGAGACATGCTTCCAGCAGGCGTGTAAAGGTAA AATCCAAGCACTCTGCGAGAATCCCGAGTGGGTACCAT TGAAGGATAACAGGATTCCTTCATACGGGGTCCTGTCT GTTGATCTGAGTCTGACGGTTGAGCTTAAAATCAAAAT TGCTTCGGGATTCGGGCCATTGATCACACACGGCTCAG GGATGGACCTATACAAATCCAACTGCAACAATGTGTAT TGGCTGACTATTCCGCCAATGAGAAATCTAGCCTTAGG CGTAATCAACACATTGGAGTGGATACCGAGATTCAAGG TTAGTCCCAACCTCTTCACTGTCCCAATTAAGGAAGCA GGCGAAGACTGCCATGCCCCAACATACCTACCTGCGGA GGTGGACGGTGATGTCAAACTCAGTTCCAACCTGGTGA	43

TABLE 13-continued

Description	Sequence	SEQ ID NO:
	TTCTACCTGGTCAAGATCTCCAATATGTTTTGGCAACCT ACGATACCTCCAGGGTTGAGCATGCTGTGGTTTATTAC GTTTACAGCCCAAGCCGCTCATTTTCTTACTTTTATCCT TTTAGGTTGCCTATAAAGGGGGTCCCAATCGAACTACA AGTGGAATGCTTCACATGGGATCAAAAACTCTGGTGCC GTCACTTCTGTGTGCTTGCGGACTCAGAATCCGGTGGA CTTATCACTCACTCTGGGATGGTGGGCATGGGAGTCAG CTGCACAGCTACCCGGGAAGATGGAACCAATCGCAGAT AATGATAATAGGCTGGAGCCTCGGTGGCCAAGCTTCTT GCCCCTTGGGCCTCCCCCCAGCCCCTCCTCCCCTTCCTG CACCCGTACCCCCGTGGTCTTTGAATAAAGTCTGAGTG GGCGGCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAATC TAG	
GC_H_MEASLES_D8 Sequence, NT (5' UTR, ORF, 3' UTR) Sequence Length: 2065	TCAAGCTTTTGGACCCTCGTACAGAAGCTAATACGACT CACTATAGGGAAATAAGAGAGAAAAGAAGAGTAAGAA GAAATATAAGAGCCACCATGTCACCACAACGAGACCG GATAAATGCCTTCTACAAAGACAACCCCCATCCTAAGG GAAGTAGGATAGTTATTAACAGAGAACATCTTATGATT GATAGACCTTATGTTTTGCTGGCTGTTCTATTCGTCATG TTTCTGAGCTTGATCGGGTTGCTAGCCATTGCAGGCATT AGACTTCATCGGGCAGCCATCTACACCGCAGAGATCCA TAAAAGCCTCAGCACCAATCTGGATGTAACTAACTCAA TCGAGCATCAGGTTAAGGACGTGCTGACACCACTCTTC AAGATCATCGGTGATGAAGTGGGCTTGAGGACACCTCA GAGATTCACTGACCTAGTGAAGTTCATCTCTGACAAGA TTAAATTCCTTAATCCGGACAGGGAATACGACTTCAGA GATCTCACTTGGTGTATCAACCCGCCAGAGAGAATCAA ATTGGATTATGATCAATACTGTGCAGATGTGGCTGCTG AAGAACTCATGAATGCATTGGTGAACTCAACTCTACTG GAGACCAGGGCAACCAATCAGTTCCTAGCTGTCTCAAA GGGAAACTGCTCAGGGCCCACTACAATCAGAGGCCAAT TCTCAAACATGTCGCTGTCCCTGTTGGACTTGTATTTAA GTCGAGGTTACAATGTGTCATCTATAGTCACTATGACA TCCCAGGGAATGTACGGGGGAACTTACCTAGTGGAAAA GCCTAATCTGAGCAGCAAAGGGTCAGAGTTGTCACAAC TGAGCATGCACCGAGTGTTTGAAGTAGGTGTTATCAGA AATCCGGGTTTGGGGGCTCCGGTATTCCATATGACAAA CTATCTTGAGCAACCAGTCAGTAATGATTTCAGCAACT GCATGGTGGCTTTGGGGGAGCTCAAGTTCGCAGCCCTC TGTCACAGGGAAGATTCTATCACAATTCCCTATCAGGG ATCAGGGAAAGGTGTCAGCTTCCAGCTTGTCAAGCTAG GTGTCTGGAAATCCCCAACCGACATGCAATCCTGGGTC CCCCTATCAACGGATGATCCAGTGATAGACAGGCTTTA CCTCTCATCTCACAGAGGCGTTATCGCTGACAATCAAG CAAAATGGGCTGTCCCGACAACACGGACAGATGACAA GTTGCGAATGGAGACATGCTTCCAGCAGGCGTGTAAGG GTAAAATCCAAGCACTTTGCGAGAATCCCGAGTGGACA CCATTGAAGGATAACAGGATTCCTTCATACGGGGTCTT GTCTGTTGATCTGAGTCTGACAGTTGAGCTTAAAATCA AAATTGTTTCAGGATTCGGGCCATTGATCACACACGGT TCAGGGATGGACCTATACAAATCCAACCACAACAATAT GTATTGGCTGACTATCCCGCCAATGAAGAACCTGGCCT TAGGTGTAATCAACACATTGGAGTGGATACCGAGATTC AAGGTTAGTCCCAACCTCTTCACTGTTCCAATTAAGGA AGCAGGCGAGGACTGCCATGCCCCAACATACCTACCTG CGGAGGTGGATGGTGATGTCAAACTCAGTTCCAATCTG GTGATTCTACCTGGTCAAGATCTCCAATATGTTCTGGCA ACCTACGATACTTCCAGAGTTGAACATGCTGTAGTTTAT TACGTTTACAGCCCAAGCCGCTCATTTTCTTACTTTTAT CCTTTTAGGTTGCCTGTAAGGGGGGTCCCCATTGAATTA CAAGTGGAATGCTTCACATGGGACCAAAAACTCTGGTG CCGTCACTTCTGTGTGCTTGCGGACTCAGAATCTGGTGG ACATATCACTCACTCTGGGATGGTGGGCATGGGAGTCA GCTGCACAGCCACTCGGGAAGATGGAACCAGCCGCAG ATAGTGATAATAGGCTGGAGCCTCGGTGGCCAAGCTTC TTGCCCCTTGGGCCTCCCCCCAGCCCCTCCTCCCCTTCC TGCACCCGTACCCCCGTGGTCTTTGAATAAAGTCTGAG TGGGCGGC	44
GC_H_MEASLES_D8 ORF Sequence, NT	ATGTCACCACAACGAGACCGGATAAATGCCTTCTACAA AGACAACCCCCATCCTAAGGGAAGTAGGATAGTTATTA ACAGAGAACATCTTATGATTGATAGACCTTATGTTTTGC TGGCTGTTCTATTCGTCATGTTTCTGAGCTTGATCGGGT TGCTAGCCATTGCAGGCATTAGACTTCATCGGGCAGCC	45

TABLE 13-continued

Description	Sequence	SEQ ID NO:
	ATCTACACCGCAGAGATCCATAAAAGCCTCAGCACCAA	
	TCTGGATGTAACTAACTCAATCGAGCATCAGGTTAAGG	
	ACGTGCTGACACCACTCTTCAAGATCATCGGTGATGAA	
	GTGGGCTTGAGGACACCTCAGAGATTCACTGACCTAGT	
	GAAGTTCATCTCTGACAAGATTAAATTCCTTAATCCGG	
	ACAGGGAATACGACTTCAGAGATCTCACTTGGTGTATC	
	AACCCGCCAGAGAGAATCAAATTGGATTATGATCAATA	
	CTGTGCAGATGTGGCTGCTGAAGAACTCATGAATGCAT	
	TGGTGAACTCAACTCTACTGGAGACCAGGGCAACCAAT	
	CAGTTCCTAGCTGTCTCAAAGGGAAACTGCTCAGGGCC	
	CACTACAATCAGAGGCCAATTCTCAAACATGTCGCTGT	
	CCCTGTTGGACTTGTATTTAAGTCGAGGTTACAATGTGT	
	CATCTATAGTCACTATGACATCCCAGGGAATGTACGGG	
	GGAACTTACCTAGTGGAAAAGCCTAATCTGAGCAGCAA	
	AGGGTCAGAGTTGTCACAACTGAGCATGCACCGAGTGT	
	TTGAAGTAGGTGTTATCAGAAATCCGGGTTTGGGGGCT	
	CCGGTATTCCATATGACAAACTATCTTGAGCAACCAGT	
	CAGTAATGATTTCAGCAACTGCATGGTGGCTTTGGGGG	
	AGCTCAAGTTCGCAGCCCTCTGTCACAGGGAAGATTCT	
	ATCACAATTCCCTATCAGGGATCAGGGAAAGGTGTCAG	
	CTTCCAGCTTGTCAAGCTAGGTGTCTGGAAATCCCCAA	
	CCGACATGCAATCCTGGGTCCCCCTATCAACGGATGAT	
	CCAGTGATAGACAGGCTTTACCTCTCATCTCACAGAGG	
	CGTTATCGCTGACAATCAAGCAAAATGGGCTGTCCCGA	
	CAACACGGACAGATGACAAGTTGCGAATGGAGACATG	
	CTTCCAGCAGGCGTGTAAGGGTAAAATCCAAGCACTTT	
	GCGAGAATCCCGAGTGGACACCATTGAAGGATAACAG	
	GATTCCTTCATACGGGGTCTTGTCTGTTGATCTGAGTCT	
	GACAGTTGAGCTTAAAATCAAAATTGTTTCAGGATTCG	
	GGCCATTGATCACACACGGTTCAGGGATGGACCTATAC	
	AAATCCAACCACAACAATATGTATTGGCTGACTATCCC	
	GCCAATGAAGAACCTGGCCTTAGGTGTAATCAACACAT	
	TGGAGTGGATACCGAGATTCAAGGTTAGTCCCAACCTC	
	TTCACTGTTCCAATTAAGGAAGCAGGCGAGGACTGCCA	
	TGCCCCAACATACCTACCTGCGGAGGTGGATGGTGATG	
	TCAAACTCAGTTCCAATCTGGTGATTCTACCTGGTCAAG	
	ATCTCCAATATGTTCTGGCAACCTACGATACTTCCAGA	
	GTTGAACATGCTGTAGTTTATTACGTTTACAGCCCAAGC	
	CGCTCATTTTCTTACTTTTATCCTTTTAGGTTGCCTGTAA	
	GGGGGGTCCCCATTGAATTACAAGTGGAATGCTTCACA	
	TGGGACCAAAAACTCTGGTGCCGTCACTTCTGTGTGCTT	
	GCGGACTCAGAATCTGGTGGACATATCACTCACTCTGG	
	GATGGTGGGCATGGGAGTCAGCTGCACAGCCACTCGGG	
	AAGATGGAACCAGCCGCAGATAG	
GC_H_MEASLES_D8 mRNA Sequence (assumes T100 tail) Sequence Length: 2126	G*GGGAAATAAGAGAGAAAAGAAGAGTAAGAAGAAAT	46
	ATAAGAGCCACCATGTCACCACAACGAGACCGGATAA	
	ATGCCTTCTACAAAGACAACCCCCATCCTAAGGGAAGT	
	AGGATAGTTATTAACAGAGAACATCTTATGATTGATAG	
	ACCTTATGTTTTGCTGGCTGTTCTATTCGTCATGTTTCTG	
	AGCTTGATCGGGTTGCTAGCCATTGCAGGCATTAGACT	
	TCATCGGGCAGCCATCTACACCGCAGAGATCCATAAAA	
	GCCTCAGCACCAATCTGGATGTAACTAACTCAATCGAG	
	CATCAGGTTAAGGACGTGCTGACACCACTCTTCAAGAT	
	CATCGGTGATGAAGTGGGCTTGAGGACACCTCAGAGAT	
	TCACTGACCTAGTGAAGTTCATCTCTGACAAGATTAAA	
	TTCCTTAATCCGGACAGGGAATACGACTTCAGAGATCT	
	CACTTGGTGTATCAACCCGCCAGAGAGAATCAAATTGG	
	ATTATGATCAATACTGTGCAGATGTGGCTGCTGAAGAA	
	CTCATGAATGCATTGGTGAACTCAACTCTACTGGAGAC	
	CAGGGCAACCAATCAGTTCCTAGCTGTCTCAAAGGGAA	
	ACTGCTCAGGGCCCACTACAATCAGAGGCCAATTCTCA	
	AACATGTCGCTGTCCCTGTTGGACTTGTATTTAAGTCGA	
	GGTTACAATGTGTCATCTATAGTCACTATGACATCCCA	
	GGGAATGTACGGGGGAACTTACCTAGTGGAAAAGCCT	
	AATCTGAGCAGCAAAGGGTCAGAGTTGTCACAACTGAG	
	CATGCACCGAGTGTTTGAAGTAGGTGTTATCAGAAATC	
	CGGGTTTGGGGGCTCCGGTATTCCATATGACAAACTAT	
	CTTGAGCAACCAGTCAGTAATGATTTCAGCAACTGCAT	
	GGTGGCTTTGGGGGAGCTCAAGTTCGCAGCCCTCTGTC	
	ACAGGGAAGATTCTATCACAATTCCCTATCAGGGATCA	
	GGGAAAGGTGTCAGCTTCCAGCTTGTCAAGCTAGGTGT	
	CTGGAAATCCCCAACCGACATGCAATCCTGGGTCCCCC	
	TATCAACGGATGATCCAGTGATAGACAGGCTTTACCTC	
	TCATCTCACAGAGGCGTTATCGCTGACAATCAAGCAAA	
	ATGGGCTGTCCCGACAACACGGACAGATGACAAGTTGC	
	GAATGGAGACATGCTTCCAGCAGGCGTGTAAGGGTAA	

TABLE 13-continued

Description	Sequence	SEQ ID NO:
	AATCCAAGCACTTTGCGAGAATCCCGAGTGGACACCAT	
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	GTTGATCTGAGTCTGACAGTTGAGCTTAAAATCAAAAT	
	TGTTTCAGGATTCGGGCCATTGATCACACACGGTTCAG	
	GGATGGACCTATACAAATCCAACCACAACAATATGTAT	
	TGGCTGACTATCCCGCCAATGAAGAACCTGGCCTTAGG	
	TGTAATCAACACATTGGAGTGGATACCGAGATTCAAGG	
	TTAGTCCCAACCTCTTCACTGTTCCAATTAAGGAAGCA	
	GGCGAGGACTGCCATGCCCCAACATACCTACCTGCGGA	
	GGTGGATGGTGATGTCAAACTCAGTTCCAATCTGGTGA	
	TTCTACCTGGTCAAGATCTCCAATATGTTCTGGCAACCT	
	ACGATACTTCCAGAGTTGAACATGCTGTAGTTTATTAC	
	GTTTACAGCCCAAGCCGCTCATTTTCTTACTTTTATCCT	
	TTTAGGTTGCCTGTAAGGGGGGTCCCCATTGAATTACA	
	AGTGGAATGCTTCACATGGGACCAAAAACTCTGGTGCC	
	GTCACTTCTGTGTGCTTGCGGACTCAGAATCTGGTGGA	
	CATATCACTCACTCTGGGATGGTGGGCATGGGAGTCAG	
	CTGCACAGCCACTCGGGAAGATGGAACCAGCCGCAGA	
	TAGTGATAATAGGCTGGAGCCTCGGTGGCCAAGCTTCT	
	TGCCCCTTGGGCCTCCCCCCAGCCCCTCCTCCCCTTCCT	
	GCACCCGTACCCCCGTGGTCTTTGAATAAAGTCTGAGT	
	GGGCGGCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAT	
	CTAG	
	MeV mRNA Sequences	
GC_F_MEASLES_B3.1 Sequence, NT (5' UTR, ORF, 3' UTR) Sequence Length: 1864	UCAAGCUUUUGGACCCUCGUACAGAAGCUAAUACGAC	69
	UCACUAUAGGGAAAUAAGAGAGAAAAGAAGAGUAAG	
	AAGAAAUAUAAGAGCCACCAUGGGUCUCAAGGUGAA	
	CGUCUCUGCCGUAUUCAUGGCAGUACUGUUAACUCUC	
	CAAACACCCGCCGGUCAAAUUCAUUGGGGCAAUCUCU	
	CUAAGAUAGGGGUAGUAGGAAUAGGAAGUGCAAGCU	
	ACAAAGUUAUGACUCGUUCCAGCCAUCAAUCAUUAGU	
	CAUAAAAUUAAUGCCCAAUAUAACUCUCCUCAAUAAC	
	UGCACGAGGGUAGAGAUUGCAGAAUACAGGAGACUA	
	CUAAGAACAGUUUUGGAACCAAUUAGGGAUGCACUU	
	AAUGCAAUGACCCAGAACAUAAGGCCGGUUCAGAGCG	
	UAGCUUCAAGUAGGAGACACAAGAGAUUUGCGGGAG	
	UAGUCCUGGCAGGUGCGGCCCUAGGUGUUGCCACAGC	
	UGCUCAGAUAACAGCCGGCAUUGCACUUCACCGGUCC	
	AUGCUGAACUCUCAGGCCAUCGACAAUCUGAGAGCGA	
	GCCUGGAAACUACUAAUCAGGCAAUUGAGGCAAUCAG	
	ACAAGCAGGGCAGGAGAUGAUAUUGGCUGUUCAGGG	
	UGUCCAAGACUACAUCAAUAAUGAGCUGAUACCGUCU	
	AUGAACCAGCUAUCUUGUGAUCUAAUCGGUCAGAAGC	
	UCGGGCUCAAAUUGCUUAGAUACUAUACAGAAAUCCU	
	GUCAUUAUUUGGCCCCAGCCUACGGGACCCCAUAUCU	
	GCGGAGAUAUCUAUCCAGGCUUUGAGUUAUGCACUU	
	GGAGGAGAUAUCAAUAAGGUGUUAGAAAAGCUCGGA	
	UACAGUGGAGGCGAUUUACUAGGCAUCUUAGAGAGC	
	AGAGGAAUAAAGGCUCGGAUAACUCACGUCGACACAG	
	AGUCCUACUUCAUAGUCCUCAGUAUAGCCUAUCCGAC	
	GCUGUCCGAGAUUAAGGGGGUGAUUGUCCACCGGCUA	
	GAGGGGGUCUCGUACAACAUAGGCUCUCAAGAGUGG	
	UAUACCACUGUGCCCAAGUAUGUUGCAACCCAAGGGU	
	ACCUUAUCUCGAAUUUUGAUGAGUCAUCAUGUACUU	
	UCAUGCCAGAGGGGACUGUGUGCAGCCAAAAUGCCUU	
	GUACCCGAUGAGUCCUCUGCUCCAAGAAUGCCUCCGG	
	GGGUCCACCAAGUCCUGUGCUCGUACACUCGUAUCCG	
	GGUCUUUUGGGAACCGGUUCAUUUUAUCACAAGGGA	
	ACCUAAUAGCCAAUUGUGCAUCAAUUCUUUGUAAGU	
	GUUACACAACAGGUACGAUUAUUAAUCAAGACCCUGA	
	CAAGAUCCUAACAUACAUUGCUGCCGAUCGCUGCCCG	
	GUAGUCGAGGUGAACGGCGUGACCAUCCAAGUCGGGA	
	GCAGGAGGUAUCCAGACGCUGUGUACUUGCACAGAAU	
	UGACCUCGGUCCUCCCAUAUCAUUGGAGAGGUUGGAC	
	GUAGGGACAAAUCUGGGGAAUGCAAUUGCCAAAUUG	
	GAGGAUGCCAAGGAAUUGUUGGAAUCAUCGGACCAG	
	AUAUUGAGAAGUAUGAAAGGUUUAUCGAGCACUAGC	
	AUAGUCUACAUCCUGAUUGCAGUGUGUCUUGGAGGG	
	UUGAUAGGGAUCCCCACUUUAAUAUGUUGCUGCAGG	
	GGGCGUUGUAACAAAAAGGGAGAACAAGUUGGUAUG	
	UCAAGACCAGGCCUAAAGCCUGACCUUACAGGAACAU	
	CAAAAUCCUAUGUAAGAUCGCUUUGAUGAUAAUAGG	
	CUGGAGCCUCGGUGGCCAAGCUUCUUGCCCCUUGGGC	

TABLE 13-continued

Description	Sequence	SEQ ID NO:
	CUCCCCCCAGCCCCUCCUCCCCUUCCUGCACCCGUACC CCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGGC	
GC_F_MEASLES_B3.1 ORF Sequence, NT	AUGGGUCUCAAGGUGAACGUCUCUGCCGUAUUCAUGG CAGUACUGUUAACUCUCCAAACACCCGCCGGUCAAAU UCAUUGGGGCAAUCUCUCUAAGAUAGGGGUAGUAGG AAUAGGAAGUGCAAGCUACAAAGUUAUGACUCGUUC CAGCCAUCAAUCAUUAGUCAUAAAAUUAAUGCCCAAU AUAACUCUCCUCAAUAACUGCACGAGGGUAGAGAUUG CAGAAUACAGGAGACUACUAAGAACAGUUUUGGAAC CAAUUAGGGAUGCACUUAAUGCAAUGACCCAGAACAU AAGGCCGGUUCAGAGCGUAGCUUCAAGUAGGAGACAC AAGAGAUUUGCGGGAGUAGUCCUGGCAGGUGCGGCCC UAGGUGUUGCCACAGCUGCUCAGAUAACAGCCGGCAU UGCACUUCACCGGUCCAUGCUGAACUCUCAGGCCAUC GACAAUCUGAGAGCGAGCCUGGAAACUACUAAUCAGG CAAUUGAGGCAAUCAGACAAGCAGGGCAGGAGAUGA UAUUGGCUGUUCAGGGUGUCCAAGACUACAUCAAUA AUGAGCUGAUACCGUCUAUGAACCAGCUAUCUUGUGA UCUAAUCGGUCAGAAGCUCGGGCUCAAAUUGCUUAGA UACUAUACAGAAAUCCUGUCAUUAUUUGGCCCCAGCC UACGGGACCCCAUAUCUGCGGAGAUAUCUAUCCAGGC UUUGAGUUAUGCACUUGGAGGAGAUAUCAAUAAGGU GUUAGAAAAGCUCGGAUACAGUGGAGGCGAUUUACU AGGCAUCUUAGAGAGCAGAGGAAUAAAGGCUCGGAU AACUCACGUCGACACAGAGUCCUACUUCAUAGUCCUC AGUAUAGCCUAUCCGACGCUGUCCGAGAUUAAGGGGG UGAUUGUCCACCGGCUAGAGGGGGUCUCGUACAACAU AGGCUCUCAAGAGUGGGUAUACCACUGUGCCCAAGUAU GUUGCAACCCAAGGGUACCUUAUCUCGAAUUUUGAUG AGUCAUCAUGUACUUUCAUGCCAGAGGGGACUGUGU GCAGCCAAAAUGCCUUGUACCCGAUGAGUCCUCUGCU CCAAGAAUGCCUCCGGGGGUCCACCAAGUCCUGUGCU CGUACACUCGUAUCCGGGUCUUUUGGGAACCGGUUCA UUUUAUCACAAGGGAACCUAAUAGCCAAUUGUGCAUC AAUUCUUUGUAAGUGUUACACAACGGUACGAUUAU UAAUCAAGACCCUGACAAGAUCCUAACAUACAUUGCU GCCGAUCGCUGCCCGGUAGUCGAGGUGAACGGCGUGA CCAUCCAAGUCGGGAGCAGGAGGUAUCCAGACGCUGU GUACUUGCACAGAAUUGACCUCGGUCCUCCCAUAUCA UUGGAGAGGUUGGACGUAGGGACAAAUCUGGGGAAU GCAAUUGCCAAAUUGGAGGAUGCCAAGGAAUUGUUG GAAUCAUCGGACCAGAUAUUGAGAAGUAUGAAAGGU UUAUCGAGCACUAGCAUAGUCUACAUCCUGAUUGCAG UGUGUCUUGGAGGGUUGAUAGGGAUCCCCACUUUAA UAUGUUGCUGCAGGGGGCGUUGUAACAAAAAGGGAG AACAAGUUGGUAUGUCAAGACCAGGCCUAAAGCCUGA CCUUACAGGAACAUCAAAAUCCUAUGUAAGAUCGCUU UGA	70
GC_F_MEASLES_B3.1 mRNA Sequence (assumes T100 tail) mRNA Sequence Length: 1925	G*GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAA UAUAAGAGCCACCAUGGGUCUCAAGGUGAACGUCUCU GCCGUAUUCAUGGCAGUACUGUUAACUCUCCAAACAC CCGCCGGUCAAAUUCAUUGGGGCAAUCUCUCUAAGAU AGGGGUAGUAGGAAUAGGAAGUGCAAGCUACAAAGU UAUGACUCGUUCCAGCCAUCAAUCAUUAGUCAUAAAA UUAAUGCCCAAUAUAACUCUCCUCAAUAACUGCACGA GGGUAGAGAUUGCAGAAUACAGGAGACUACUAAGAA CAGUUUUGGAACCAAUUAGGGAUGCACUUAAUGCAA UGACCCAGAACAUAAGGCCGGUUCAGAGCGUAGCUUC AAGUAGGAGACACAAGAGAUUUGCGGGAGUAGUCCU GGCAGGUGCGGCCCUAGGUGUUGCCACAGCUGCUCAG AUAACAGCCGGCAUUGCACUUCACCGGUCCAUGCUGA ACUCUCAGGCCAUCGACAAUCUGAGAGCGAGCCUGGA AACUACUAAUCAGGCAAUUGAGGCAAUCAGACAAGCA GGGCAGGAGAUGAUAUUGGCUGUUCAGGGUGUCCAA GACUACAUCAAUAAUGAGCUGAUACCGUCUAUGAACC AGCUAUCUUGUGAUCUAAUCGGUCAGAAGCUCGGGCU CAAAUUGCUUAGAUACUAUACAGAAAUCCUGUCAUU AUUUGGCCCCAGCCUACGGGACCCCAUAUCUGCGGAG AUAUCUAUCCAGGCUUUGAGUUAUGCACUUGGAGGA GAUAUCAAUAAGGUGUUAGAAAAGCUCGGAUACAGU GGAGGCGAUUUACUAGGCAUCUUAGAGAGCAGAGGA AUAAAGGCUCGGAUAACUCACGUCGACACAGAGUCCU ACUUCAUAGUCCUCAGUAUAGCCUAUCCGACGCUGUC CGAGAUUAAGGGGGUGAUUGUCCACCGGCUAGAGGG GGUCUCGUACAACAUAGGCUCUCAAGAGUGGUAUACC	71

TABLE 13-continued

Description	Sequence	SEQ ID NO:
	ACUGUGCCCAAGUAUGUUGCAACCCAAGGGUACCUUA	
	UCUCGAAUUUUGAUGAGUCAUCAUGUACUUUCAUGCC	
	AGAGGGGACUGUGUGCAGCCAAAAUGCCUUGUACCCG	
	AUGAGUCCUCUGCUCCAAGAAUGCCUCCGGGGGUCCA	
	CCAAGUCCUGUGCUCGUACACUCGUAUCCGGGUCUUU	
	UGGGAACCGGUUCAUUUUAUCACAAGGGAACCUAAU	
	AGCCAAUUGUGCAUCAAUUCUUUGUAAGUGUUACAC	
	AACAGGUACGAUUAUUAAUCAAGACCCUGACAAGAUC	
	CUAACAUACAUUGCUGCCGAUCGCUGCCCGGUAGUCG	
	AGGUGAACGGCGUGACCAUCCAAGUCGGGAGCAGGAG	
	GUAUCCAGACGCUGUGUACUUGCACAGAAUUGACCUC	
	GGUCCUCCCAUAUCAUUGGAGAGGUUGGACGUAGGG	
	ACAAAUCUGGGGAAUGCAAUUGCCAAAUUGGAGGAU	
	GCCAAGGAAUUGUUGGAAUCAUCGGACCAGAUAUUG	
	AGAAGUAUGAAAGGUUUAUCGAGCACUAGCAUAGUC	
	UACAUCCUGAUUGCAGUGUGUCUUGGAGGGUUGAUA	
	GGGAUCCCCACUUUAAUAUGUUGCUGCAGGGGGCGUU	
	GUAACAAAAAGGGAGAACAAGUUGGUAUGUCAAGAC	
	CAGGCCUAAAGCCUGACCUUACAGGAACAUCAAAAUC	
	CUAUGUAAGAUCGCUUUGAUGAUAAUAGGCUGGAGC	
	CUCGGUGGCCAAGCUUCUUGCCCCUUGGGCCUCCCCC	
	CAGCCCCUCCUCCCCUUCCUGCACCCGUACCCCCGUGG	
	UCUUUGAAUAAAGUCUGAGUGGGCGGCAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAUCUAG	
GC_F_MEASLES_D8 Sequence, NT (5' UTR, ORF, 3' UTR) Sequence Length: 1864	UCAAGCUUUUGGACCCUCGUACAGAAGCUAAUACGAC	72
	UCACUAUAGGGAAAUAAGAGAGAAAAGAAGAGUAAG	
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	CGUCUCUGUCAUAUUCAUGGCAGUACUGUUAACUCUU	
	CAAACACCCACCGGUCAAAUCCAUUGGGGCAAUCUCU	
	CUAAGAUAGGGGUGGUAGGGGUAGGAAGUGCAAGCU	
	ACAAAGUUAUGACUCGUUCCAGCCAUCAAUCAUUAGU	
	CAUAAAGUUAAUGCCCAAUAUAACUCUCCUCAACAAU	
	UGCACGAGGGUAGGGAUUGCAGAAUACAGGAGACUA	
	CUGAGAACAGUUCUGGAACCAAUUAGAGAUGCACUU	
	AAUGCAAUGACCCAGAAUAUAAGACCGGUUCAGAGU	
	GUAGCUUCAAGUAGGAGACACAAGAGAUUUGCGGGA	
	GUUGUCCUGGCAGGUGCGGCCCUAGGCGUUGCCACAG	
	CUGCUCAAAUAACAGCCGGUAUUGCACUUCACCAGUC	
	CAUGCUGAACUCUCAAGCCAUCGACAAUCUGAGAGCG	
	AGCCUAGAAACUACUAAUCAGGCAAUUGAGGCAAUCA	
	GACAAGCAGGGCAGGAGAUGAUAUUGGCUGUUCAGG	
	GUGUCCAAGACUACAUCAAUAAUGAGCUGAUACCGUC	
	UAUGAAUCAACUAUCUUGUGAUUUAAUCGGCCAGAA	
	GCUAGGGCUCAAAUUGCUCAGAUACUAUACAGAAAUC	
	CUGUCAUUAUUUGGCCCCAGCUUACGGGACCCCAUAU	
	CUGCGGAGAUAUCUAUCCAGGCUUUGAGCUAUGCGCU	
	UGGAGGAGAUAUCAAUAAGGUGUUGGAAAAGCUCGG	
	AUACAGUGGAGGUGAUCUACUGGGCAUCUUAGAGAG	
	CAGAGGAAUAAAGGCCCGGAUAACUCACGUCGACACA	
	GAGUCCUACUUCAUUGUACUCAGUAUAGCCUAUCCGA	
	CGCUAUCCGAGAUUAAGGGGGUGAUUGUCCACCGGCU	
	AGAGGGGGUCUCGUACAACAUAGGCUCUCAAGAGUG	
	GUAUACCACUGUGCCCAAGUAUGUUGCAACCCAAGGG	
	UACCUUAUCUCGAAUUUUGAUGAGUCAUCAUGCACUU	
	UCAUGCCAGAGGGGACUGUGUGCAGCCAGAAUGCCUU	
	GUACCCGAUGAGUCCUCUGCUCCAAGAAUGCCUCCGG	
	GGGUCCACUAAGUCCUGUGCUCGUACACUCGUAUCCG	
	GGUCUUUCGGGAACCGGUUCAUUUUAUCACAGGGGA	
	ACCUAAUAGCCAAUUGUGCAUCAAUCCUUUGCAAGUG	
	UUACACAACAGGAACAAUCAUUAAUCAAGACCCUGAC	
	AAGAUCCUAACAUACAUUGCUGCCGAUCACUGCCCGG	
	UGGUCGAGGUGAAUGGCGUGACCAUCCAAGUCGGGA	
	GCAGGAGGUAUCCGGACGCUGUGUACUUGCACAGGAU	
	UGACCUCGGUCCUCCCAUAUCUUUGGAGAGGUUGGAC	
	GUAGGGACAAAUCUGGGGAAUGCAAUUGCUAAGUUG	
	GAGGAUGCCAAGGAAUUGUUGGAGUCAUCGGACCAG	
	AUAUUGAGGAGUAUGAAAGGUUUAUCGAGCACUAGU	
	AUAGUUUACAUCCUGAUUGCAGUGUGUCUUGGAGGA	
	UUGAUAGGGAUCCCCGCUUUAAUAUGUUGCUGCAGG	
	GGGCGUUGUAACAAGAAGGGAGAACAAGUUGGUAUG	
	UCAAGACCAGGCCUAAAGCCUGAUCUUACAGGAACAU	
	CAAAAUCCUAUGUAAGGUCACUCUGAUGAUAAUAGG	
	CUGGAGCCUCGGUGGCCAAGCUUCUUGCCCCUUGGGC	
	CUCCCCCCAGCCCCUCCUCCCCUUCCUGCACCCGUACC	

TABLE 13-continued

Description	Sequence	SEQ ID NO:
	CCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGGC	
GC_F_MEASLES_D8 ORF Sequence, NT	AUGGGUCUCAAGGUGAACGUCUCUGUCAUAUUCAUG GCAGUACUGUUAACUCUUCAAACACCCACCGGUCAAA UCCAUUGGGGCAAUCUCUCUAAGAUAGGGGUGGUAG GGGUAGGAAGUGCAAGCUACAAAGUUAUGACUCGUU CCAGCCAUCAAUCAUUAGUCAUAAAGUUAAUGCCCAA UAUAACUCUCCCUCAACAAUUGCACGAGGGUAGGGAUU GCAGAAUACAGGAGACUACUGAGAACAGUUCUGGAA CCAAUUAGAGAUGCACUUAAUGCAAUGACCCAGAAUA UAAGACCGGUUCAGAGUGUAGCUUCAAGUAGGAGAC ACAAGAGAUUUGCGGGAGUUGUCCUGGCAGGUGCGG CCCUAGGCGUUGCCACAGCUGCUCAAAUAACAGCCGG UAUUGCACUUCACCAGUCCAUGCUGAACUCUCAAGCC AUCGACAAUCUGAGAGCGAGCCUAGAAACUACUAAUC AGGCAAUUGAGGCAAUCAGACAAGCAGGGCAGGAGA UGAUAUUGGCUGUUCAGGGUGUCCAAGACUACAUCA AUAAUGAGCUGAUACCGUCUAUGAAUCAACUAUCUU GUGAUUUAAUCGGCCAGAAGCUAGGGCUCAAAUUGC UCAGAUACUAUACAGAAAUCCUGUCAUUAUUUGGCCC CAGCUUACGGGACCCCAUAUCUGCGGAGAUAUCUAUC CAGGCUUUGAGCUAUGCGCUUGGAGGAGAUAUCAAU AAGGUGUUGGAAAAGCUCGGAUACAGUGGAGGUGAU CUACUGGGCAUCUUAGAGAGCAGAGGAAUAAAGGCCC GGAUAACUCACGUCGACACAGAGUCCUACUUCAUUGU ACUCAGUAUAGCCUAUCCGACGCUAUCCGAGAUUAAG GGGGUGAUUGUCCACCGGCUAGAGGGGGUCUCGUACA ACAUAGGCUCUCAAGAGUGGGUAUACCACUGUGCCCAA GUAUGUUGCAACCCAAGGGUACCUUAUCUCGAAUUUU GAUGAGUCAUCAUGCACUUUCAUGCCAGAGGGGACUG UGUGCAGCCAGAAUGCCUUGUACCCGAUGAGUCCUCU GCUCCAAGAAUGCCUCCGGGGGUCCACUAAGUCCUGU GCUCGUACACUCGUAUCCGGGUCUUUCGGGAACCGGU UCAUUUUAUCACAGGGGAACCUAAUAGCCAAUUGUGC AUCAAUCCUUUGCAAGUGUUACACAACAGGAACAAUC AUUAAUCAAGACCCUGACAAGAUCCUAACAUACAUUG CUGCCGAUCACUGCCCGGUGGUCGAGGUGAAUGGCGU GACCAUCCAAGUCGGGAGCAGGAGGUAUCCGGACGCU GUGUACUUGCACAGGAUUGACCUCGGUCCUCCCAUAU CUUUGGAGAGGUUGGACGUAGGGACAAAUCUGGGGA AUGCAAUUGCUAAGUUGGAGGAUGCCAAGGAAUUGU UGGAGUCAUCGGACCAGAUAUUGAGGAGUAUGAAAG GUUUAUCGAGCACUAGUAUAGUUUACAUCCUGAUUG CAGUGUGUCUUGGAGGAUUGAUAGGGAUCCCCGCUU UAAUAUGUUGCUGCAGGGGGCGUUGUAACAAGAAGG GAGAACAAGUUGGUAUGUCAAGACCAGGCCUAAAGCC UGAUCUUACAGGAACAUCAAAAUCCUAUGUAAGGUC ACUCUGA	73
GC_F_MEASLES_D8 mRNA Sequence (assumes T100 tail) Sequence Length: 1925	G*GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAA UAUAAGAGCCACCAUGGGUCUCAAGGUGAACGUCUCU GUCAUAUUCAUGGCAGUACUGUUAACUCUUCAAACAC CCACCGGUCAAAUCCAUUGGGGCAAUCUCUCUAAGAU AGGGGUGGUAGGGGUAGGAAGUGCAAGCUACAAAGU UAUGACUCGUUCCAGCCAUCAAUCAUUAGUCAUAAAG UUAAUGCCCAAUAUAACUCUCCUCAACAAUUGCACGA GGGUAGGGAUUGCAGAAUACAGGAGACUACUGAGAA CAGUUCUGGAACCAAUUAGAGAUGCACUUAAUGCAA UGACCCAGAAUAUAAGACCGGUUCAGAGUGUAGCUUC AAGUAGGAGACACAAGAGAUUUGCGGGAGUUGUCCU GGCAGGUGCGGCCCUAGGCGUUGCCACAGCUGCUCAA AUAACAGCCGGUAUUGCACUUCACCAGUCCAUGCUGA ACUCUCAAGCCAUCGACAAUCUGAGAGCGAGCCUAGA AACUACUAAUCAGGCAAUUGAGGCAAUCAGACAAGCA GGGCAGGAGAUGAUAUUGGCUGUUCAGGGUGUCCAA GACUACAUCAAUAAUGAGCUGAUACCGUCUAUGAAUC AACUAUCUUGUGAUUUAAUCGGCCAGAAGCUAGGGC UCAAAUUGCUCAGAUACUAUACAGAAAUCCUGUCAUU AUUUGGCCCCAGCUUACGGGACCCCAUAUCUGCGGAG AUAUCUAUCCAGGCUUUGAGCUAUGCGCUUGGAGGA GAUAUCAAUAAGGUGUUGGAAAAGCUCGGAUACAGU GGAGGUGAUCUACUGGGCAUCUUAGAGAGCAGAGGA AUAAAGGCCCGGAUAACUCACGUCGACACAGAGUCCU ACUUCAUUGUACUCAGUAUAGCCUAUCCGACGCUAUC CGAGAUUAAGGGGGUGAUUGUCCACCGGCUAGAGGG GGUCUCGUACAACAUAGGCUCUCAAGAGUGGUAUACC ACUGUGCCCAAGUAUGUUGCAACCCAAGGGUACCUUA	74

TABLE 13-continued

Description	Sequence	SEQ ID NO:
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	AGAGGGGACUGUGUGCAGCCAGAAUGCCUUGUACCCG	
	AUGAGUCCUCUGCUCCAAGAAUGCCUCCGGGGGUCCA	
	CUAAGUCCUGUGCUCGUACACUCGUAUCCGGGUCUUU	
	CGGGAACCGGUUCAUUUUAUCACAGGGGAACCUAAUA	
	GCCAAUUGUGCAUCAAUCCUUUGCAAGUGUUACACAA	
	CAGGAACAAUCAUUAAUCAAGACCCUGACAAGAUCCU	
	AACAUACAUUGCUGCCGAUCACUGCCCGGUGGUCGAG	
	GUGAAUGGCGUGACCAUCCAAGUCGGGAGCAGGAGG	
	UAUCCGGACGCUGUGUACUUGCACAGGAUUGACCUCG	
	GUCCUCCCAUAUCUUUGGAGAGGUUGGACGUAGGGAC	
	AAAUCUGGGGAAUGCAAUUGCUAAGUUGGAGGAUGC	
	CAAGGAAUUGUUGGAGUCAUCGGACCAGAUAUUGAG	
	GAGUAUGAAAGGUUUAUCGAGCACUAGUAUAGUUUA	
	CAUCCUGAUUGCAGUGUGUCUUGGAGGAUUGAUAGG	
	GAUCCCCGCUUUAAUAUGUUGCUGCAGGGGGCGUUGU	
	AACAAGAAGGGAGAACAAGUUGGUAUGUCAAGACCA	
	GGCCUAAAGCCUGAUCUUACAGGAACAUCAAAAUCCU	
	AUGUAAGGUCACUCUGAUGAUAAUAGGCUGGAGCCU	
	CGGUGGCCAAGCUUCUUGCCCCUUGGGCCUCCCCCCA	
	GCCCCUCCUCCCCUUCCUGCACCCGUACCCCCGUGGUC	
	UUUGAAUAAAGUCUGAGUGGGCGGCAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAUCUAG	
GC_H_MEASLES_B3	UCAAGCUUUUGGACCCUCGUACAGAAGCUAAUACGAC	75
Sequence, NT (5'	UCACUAUAGGGAAAUAAGAGAGAAAAGAAGAGUAAG	
UTR, ORF, 3'	AAGAAAUAUAAGAGCCACCAUGUCACCGCAACGAGAC	
UTR)	CGGAUAAAUGCCUUCUACAAAGAUAACCCUUAUCCCA	
Sequence Length:	AGGGAAGUAGGAUAGUUAUUAACAGAGAACAUCUUA	
2065	UGAUUGACAGACCCUAUGUUCUGCUGGCUGUUCUGUU	
	CGUCAUGUUUCUGAGCUUGAUCGGAUUGCUGGCAAU	
	UGCAGGCAUUAGACUUCAUCGGGCAGCCAUCUACACC	
	GCGGAGAUCCAUAAAAGCCUCAGUACCAAUCUGGAUG	
	UGACUAACUCCAUCGAGCAUCAGGUCAAGGACGUGCU	
	GACACCACUCUUUAAAAUCAUCGGGGAUGAAGUGGGC	
	CUGAGAACACCUCAGAGAUUCACUGACCUAGUGAAAU	
	UCAUCUCGGACAAGAUUAAAUUCCUUAAUCCGGAUAG	
	GGAGUACGACUUCAGAGAUCUCACUUGGUGCAUCAAC	
	CCGCCAGAGAGGAUCAAACUAGAUUAUGAUCAAUACU	
	GUGCAGAUGUGGCUGCUGAAGAGCUCAUGAAUGCAU	
	UGGUGAACUCAACUCUACUGGAGACCAGAACAACCAC	
	UCAGUUCCUAGCUGUCUCAAAGGGAAACUGCUCAGGG	
	CCCACUACAAUCAGAGGUCAAUUCUCAAACAUGUCGC	
	UGUCCUUGUUGGACUUGUACUUAGGUCGAGGUUACA	
	AUGUGUCAUCUAUAGUCACUAUGACAUCCCAGGGAAU	
	GUAUGGGGGAACCUACCUAGUUGAAAAGCCUAAUCU	
	GAACAGCAAAGGGUCAGAGUUGUCACAACUGAGCAU	
	GUACCGAGUGUUUGAAGUAGGUGUGAUCAGAAACCC	
	GGGUUUGGGGGCUCCGGUGUUCCAUAUGACAAACUA	
	UUUUGAGCAACCAGUCAGUAAUGGUCUCGGCAACUGU	
	AUGGUGGCUUUGGGGGAGCUCAAACUCGCAGCCCUUU	
	GUCACGGGGACGAUUCUAUCAUAAUUCCCUAUCAGGG	
	AUCAGGGAAAGGUGUCAGCUUCCAGCUCGUCAAGCUG	
	GGUGUCUGGAAAUCCCCAACCGACAUGCAAUCCUGGG	
	UCCCCUUAUCAACGGAUGAUCCAGUGGUAGACAGGCU	
	UUACCUCUCAUCUCACAGAGGUGUCAUCGCUGACAAU	
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	ACAAGUUGCGAAUGGAGACAUGCUUCCAGCAGGCGUG	
	UAAAGGUAAAAUCCAAGCACUCUGCGAGAAUCCCGAG	
	UGGGUACCAUUGAAGGAUAACAGGAUUCCUUCAUAC	
	GGGGUCCUGUCUGUUGAUCUGAGUCUGACGGUUGAG	
	CUUAAAAUCAAAAUUGCUUCGGGAUUCGGGCCAUUG	
	AUCACACACGGCUCAGGGAUGGACCUAUACAAAUCCA	
	ACUGCAACAAUGUGUAUUGGCUGACUAUUCCGCCAAU	
	GAGAAAUCUAGCCUUAGGCGUAAUCAACACAUUGGA	
	GUGGAUACCGAGAUUCAAGGUUAGUCCCAACCUCUUC	
	ACUGUCCCAAUUAAGGAAGCAGGCGAAGACUGCCAUG	
	CCCCAACAUACCUACCUGCGGAGGUGGACGGUGAUGU	
	CAAACUCAGUUCCAACCUGGUGAUUCUACCUGGUCAA	
	GAUCUCCAAUAUGUUUUGGCAACCUACGAUACCUCCA	
	GGGUUGAGCAUGCUGUGGUUUAUUACGUUUACAGCC	
	CAAGCCGCUCAUUUUCUUACUUUUAUCCUUUUAGGUU	
	GCCUAUAAAGGGGGUCCCAAUCGAACUACAAGUGGAA	
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	UCUGUGUGCUUGCGGACUCAGAAUCCGGUGGACUUAU	

TABLE 13-continued

Description	Sequence	SEQ ID NO:
	CACUCACUCUGGGAUGGUGGGCAUGGGAGUCAGCUGC ACAGCUACCCGGGAAGAUGGAACCAAUCGCAGAUAAU GAUAAUAGGCUGGAGCCUCGGUGGCCAAGCUUCUUGC CCCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGC ACCCGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUG GGCGGC	
GC_H_MEASLES_B3 ORF Sequence, NT	AUGUCACCGCAACGAGACCGGAUAAAUGCCUUCUACA AAGAUAACCCUUAUCCCAAGGGAAGUAGGAUAGUUA UUAACAGAGAACAUCUUAUGAUUGACAGACCCUAUG UUCUGCUGGCUGUUCUGUUCGUCAUGUUUCUGAGCUU GAUCGGAUUGCUGGCAAUUGCAGGCAUUAGACUUCA UCGGGCAGCCAUCUACACCGCGGAGAUCCAUAAAAGC CUCAGUACCAAUCUGGAUGUGACUAACUCCAUCGAGC AUCAGGUCAAGGACGUGCUGACACCACUCUUUAAAAU CAUCGGGGAUGAAGUGGGCCUGAGAACACCUCAGAGA UUCACUGACCUAGUGAAAUUCAUCUCGGACAAGAUUA AAUUCCUUAAUCCGGAUAGGGAGUACGACUUCAGAG AUCUCACUUGGUGCAUCAACCCGCCAGAGAGGAUCAA ACUAGAUUAUGAUCAAUACUGUGCAGAUGUGGCUGC UGAAGAGCUCAUGAAUGCAUUGGUGAACUCAACUCU ACUGGAGACCAGAACAACCACUCAGUUCCUAGCUGUC UCAAAGGGAAACUGCUCAGGGCCCACUACAAUCAGAG GUCAAUUCUCAAACAUGUCGCUGUCCUUGUUGGACUU GUACUUAGGUCGAGGUUACAAUGUGUCAUCUAUAGU CACUAUGACAUCCCAGGGAAUGUAUGGGGGAACCUAC CUAGUUGAAAAGCCUAAUCUGAACAGCAAAGGGUCA GAGUUGUCACAACUGAGCAUGUACCGAGUGUUUGAA GUAGGUGUGAUCAGAAACCCGGGUUUGGGGGCUCCG GUGUUCCAUAUGACAAACUAUUUUGAGCAACCAGUCA GUAAUGGUCUCGGCAACUGUAUGGUGGCUUUGGGGG AGCUCAAACUCGCAGCCCUUUGUCACGGGGACGAUUC UAUCAUAAUUCCCUAUCAGGGAUCAGGGAAAGGUGU CAGCUUCCAGCUCGUCAAGCUGGGUGUCUGGAAAUCC CCAACCGACAUGCAAUCCUGGGUCCCCUUAUCAACGG AUGAUCCAGUGGUAGACAGGCUUUACCUCUCAUCUCA CAGAGGUGUCAUCGCUGACAAUCAAGCAAAAUGGGCU GUCCCGACAACACGAACAGAUGACAAGUUGCGAAUGG AGACAUGCUUCCAGCAGGCGUGUAAAGGUAAAAUCCA AGCACUCUGCGAGAAUCCCGAGUGGGUACCAUUGAAG GAUAACAGGAUUCCUUCAUACGGGGUCCUGUCUGUUG AUCUGAGUCUGACGGUUGAGCUUAAAAUCAAAAUUG CUUCGGGAUUCGGGCCAUUGAUCACACACGGCUCAGG GAUGGACCUAUACAAAUCCAACUGCAACAAUGUGUAU UGGCUGACUAUUCCGCCAAUGAGAAAUCUAGCCUUAG GCGUAAUCAACACAUUGGAGUGGAUACCGAGAUUCA AGGUUAGUCCCAACCUCUUCACUGUCCCAAUUAAGGA AGCAGGCGAAGACUGCCAUGCCCCAACAUACCUACCU GCGGAGGUGGACGGUGAUGUCAAACUCAGUUCCAACC UGGUGAUUCUACCUGGUCAAGAUCUCCAAUAUGUUU UGGCAACCUACGAUACCUCCAGGGUUGAGCAUGCUGU GGUUUAUUACGUUUACAGCCCAAGCCGCUCAUUUUCU UACUUUUAUCCUUUUAGGUUGCCUAUAAAGGGGGUC CCAAUCGAACUACAAGUGGAAUGCUUCACAUGGGAUC AAAAACUCUGGUGCCGUCACUUCUGUGUGCUUGCGGA CUCAGAAUCCGGUGGACUUAUCACUCACUCUGGGAUG GUGGGCAUGGGAGUCAGCUGCACAGCUACCCGGGAAG AUGGAACCAAUCGCAGAUAA	76
GC_H_MEASLES_B3 mRNA Sequence (assumes T100 Tail) Sequence Length: 2126	G*GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAA UAUAAGAGCCACCAUGUCACCGCAACGAGACCGGAUA AAUGCCUUCUACAAAGAUAACCCUUAUCCCAAGGGAA GUAGGAUAGUUAUUAACAGAGAACAUCUUAUGAUUG ACAGACCCUAUGUUCUGCUGGCUGUUCUGUUCGUCAU GUUUCUGAGCUUGAUCGGAUUGCUGGCAAUUGCAGG CAUUAGACUUCAUCGGGCAGCCAUCUACACCGCGGAG AUCCAUAAAAGCCUCAGUACCAAUCUGGAUGUGACUA ACUCCAUCGAGCAUCAGGUCAAGGACGUGCUGACACC ACUCUUUAAAAUCAUCGGGGAUGAAGUGGGCCUGAG AACACCUCAGAGAUUCACUGACCUAGUGAAAUUCAUC UCGGACAAGAUUAAAUUCCUUAAUCCGGAUAGGGAG UACGACUUCAGAGAUCUCACUUGGUGCAUCAACCCGC CAGAGAGGAUCAAACUAGAUUAUGAUCAAUACUGUG CAGAUGUGGCUGCUGAAGAGCUCAUGAAUGCAUUGG UGAACUCAACUCUACUGGAGACCAGAACAACCACUCA GUUCCUAGCUGUCUCAAAGGGAAACUGCUCAGGGCCC ACUACAAUCAGAGGUCAAUUCUCAAACAUGUCGCUGU	77

TABLE 13-continued

Description	Sequence	SEQ ID NO:
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	UGGGGGAACCUACCUAGUUGAAAAGCCUAAUCUGAAC	
	AGCAAAGGGUCAGAGUUGUCACAACUGAGCAUGUACC	
	GAGUGUUUGAAGUAGGUGUGAUCAGAAACCCGGGUU	
	UGGGGGCUCCGGUGUUCCAUAUGACAAACUAUUUUG	
	AGCAACCAGUCAGUAAUGGUCUCGGCAACUGUAUGGU	
	GGCUUUGGGGGAGCUCAAACUCGCAGCCCUUUGUCAC	
	GGGGACGAUUCUAUCAUAAUUCCCUAUCAGGGAUCAG	
	GGAAAGGUGUCAGCUUCCAGCUCGUCAAGCUGGGUGU	
	CUGGAAAUCCCCAACCGACAUGCAAUCCUGGGUCCCC	
	UUAUCAACGGAUGAUCCAGUGGUAGACAGGCUUUACC	
	UCUCAUCUCACAGAGGUGUCAUCGCUGACAAUCAAGC	
	AAAAUGGGCUGUCCCGACAACACGAACAGAUGACAAG	
	UUGCGAAUGGAGACAUGCUUCCAGCAGGCGUGUAAA	
	GGUAAAAUCCAAGCACUCUGCGAGAAUCCCGAGUGGG	
	UACCAUUGAAGGAUAACAGGAUUCCUUCAUACGGGG	
	UCCUGUCUGUUGAUCUGAGUCUGACGGUUGAGCUUA	
	AAAUCAAAAUUGCUUCGGGAUUCGGGCCAUUGAUCAC	
	ACACGGCUCAGGGAUGGACCUAUACAAAUCCAACUGC	
	AACAAUGUGUAUUGGCUGACUAUUCCGCCAAUGAGA	
	AAUCUAGCCUUAGGCGUAAUCAACACAUUGGAGUGG	
	AUACCGAGAUUCAAGGUUAGUCCCAACCUCUUCACUG	
	UCCCAAUUAAGGAAGCAGGCGAAGACUGCCAUGCCCC	
	AACAUACCUACCUGCGGAGGUGGACGGUGAUGUCAAA	
	CUCAGUUCCAACCUGGUGAUUCUACCUGGUCAAGAUC	
	UCCAAUAUGUUUUGGCAACCUACGAUACCUCCAGGGU	
	UGAGCAUGCUGUGGUUUAUUACGUUUACAGCCCAAGC	
	CGCUCAUUUUCUUACUUUUAUCCUUUUAGGUUGCCUA	
	UAAAGGGGUCCCAAUCGAACUACAAGUGGAAUGCU	
	UCACAUGGGAUCAAAAACUCUGGUGCCGUCACUUCUG	
	UGUGCUUGCGGACUCAGAAUCCGGUGGACUUAUCACU	
	CACUCUGGGAUGGUGGGCAUGGGAGUCAGCUGCACAG	
	CUACCCGGGAAGAUGGAACCAAUCGCAGAUAAUGAUA	
	AUAGGCUGGAGCCUCGGUGGCCAAGCUUCUUGCCCCU	
	UGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACCC	
	GUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCG	
	GCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAUCUAG	
GC_H_MEASLES_D8 Sequence, NT (5' UTR, ORF, 3' UTR) Sequence Length: 2065	UCAAGCUUUUGGACCCUCGUACAGAAGCUAAUACGAC	78
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	AAGAAAUAUAAGAGCCACCAUGUCACCACAACGAGAC	
	CGGAUAAAUGCCUUCUACAAAGACAACCCCCAUCCUA	
	AGGGAAGUAGGAUAGUUAUUAACAGAGAACAUCUUA	
	UGAUUGAUAGACCUUAUGUUUUGCUGGCUGUUCUAU	
	UCGUCAUGUUUCUGAGCUUGAUCGGGUUGCUAGCCAU	
	UGCAGGCAUUAGACUUCAUCGGGCAGCCAUCUACACC	
	GCAGAGAUCCAUAAAAGCCUCAGCACCAAUCUGGAUG	
	UAACUAACUCAAUCGAGCAUCAGGUUAAGGACGUGCU	
	GACACCACUCUUCAAGAUCAUCGGUGAUGAAGUGGGC	
	UUGAGGACACCUCAGAGAUUCACUGACCUAGUGAAGU	
	UCAUCUCUGACAAGAUUAAAUUCCUUAAUCCGGACAG	
	GGAAUACGACUUCAGAGAUCUCACUUGGUGUAUCAAC	
	CCGCCAGAGAGAAUCAAAUUGGAUUAUGAUCAAUAC	
	UGUGCAGAUGUGGCUGCUGAAGAACUCAUGAAUGCA	
	UUGGUGAACUCAACUCUACUGGAGACCAGGGCAACCA	
	AUCAGUUCCUAGCUGUCUCAAAGGGAAACUGCUCAGG	
	GCCCACUACAAUCAGAGGCCAAUUCUCAAACAUGUCG	
	CUGUCCCUGUUGGACUUGUAUUUAAGUCGAGGUUAC	
	AAUGUGUCAUCUAUAGUCACUAUGACAUCCCAGGGAA	
	UGUACGGGGGAACUUACCUAGUGGAAAAGCCUAAUC	
	UGAGCAGCAAAGGGUCAGAGUUGUCACAACUGAGCA	
	UGCACCGAGUGUUUGAAGUAGGUGUUAUCAGAAAUC	
	CGGGUUUGGGGGCUCCGGUAUUCCAUAUGACAAACUA	
	UCUUGAGCAACCAGUCAGUAAUGAUUUCAGCAACUGC	
	AUGGUGGCUUUGGGGGAGCUCAAGUUCGCAGCCCUCU	
	GUCACAGGGAAGAUUCUAUCACAAUUCCCUAUCAGGG	
	AUCAGGGAAAGGUGUCAGCUUCCAGCUUGUCAAGCUA	
	GGUGUCUGGAAAUCCCCAACCGACAUGCAAUCCUGGG	
	UCCCCCUAUCAACGGAUGAUCCAGUGAUAGACAGGCU	
	UUACCUCUCAUCUCACAGAGGCGUUAUCGCUGACAAU	
	CAAGCAAAAUGGGCUGUCCCGACAACACGGACAGAUG	
	ACAAGUUGCGAAUGGAGACAUGCUUCCAGCAGGCGUG	
	UAAGGGUAAAAUCCAAGCACUUUGCGAGAAUCCCGAG	
	UGGACACCAUUGAAGGAUAACAGGAUUCCUUCAUACG	

TABLE 13-continued

Description	Sequence	SEQ ID NO:
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GC_H_MEASLES_D8 ORF Sequence, NT	AUGUCACCACAACGAGACCGGAUAAAUGCCUUCUACA AAGACAACCCCCAUCCUAAGGGAAGUAGGAUAGUUAU UAACAGAGAACAUCUUAUGAUUGAUAGACCUUAUGU UUUGCUGGCUGUUCUAUUCGUCAUGUUUCUGAGCUU GAUCGGGUUGCUAGCCAUUGCAGGCAUUAGACUUCAU CGGGCAGCCAUCUACACCGCAGAGAUCCAUAAAAGCC UCAGCACCAAUCUGGAUGUAACUAACUCAAUCGAGCA UCAGGUUAAGGACGUGCUGACACCACUCUUCAAGAUC AUCGGUGAUGAAGUGGGCUUGAGGACACCUCAGAGA UUCACUGACCUAGUGAAGUUCAUCUCUGACAAGAUUA AAUUCCUUAAUCCGGACAGGGAAUACGACUUCAGAGA UCUCACUUGGUGUAUCAACCCGCCAGAGAGAAUCAAA UUGGAUUAUGAUCAAUACUGUGCAGAUGUGGCUGCU GAAGAACUCAUGAAUGCAUUGGUGAACUCAACUCUAC UGGAGACCAGGGCAACCAAUCAGUUCCUAGCUGUCUC AAAGGGAAACUGCUCAGGGCCCACUACAAUCAGAGGC CAAUUCUCAAACAUGUCGCUGUCCCUGUUGGACUUGU AUUUAAGUCGAGGUUACAAUGUGUCAUCUAUAGUCA CUAUGACAUCCCAGGGAAUGUACGGGGGAACUUACCU AGUGGAAAAGCCUAAUCUGAGCAGCAAAGGGUCAGA GUUGUCACAACUGAGCAUGCACCGAGUGUUUGAAGU AGGUGUUAUCAGAAAUCCGGGUUUGGGGGCUCCGGU AUUCCAUAUGACAAACUAUCUUGAGCAACCAGUCAGU AAUGAUUUCAGCAACUGCAUGGUGGCUUUGGGGGAG CUCAAGUUCGCAGCCCUCUGUCACAGGGAAGAUUCUA UCACAAUUCCCUAUCAGGGAUCAGGGAAAGGUGUCAG CUUCCAGCUUGUCAAGCUAGGUGUCUGGAAAUCCCCA ACCGACAUGCAAUCCUGGGUCCCCCUAUCAACGGAUG AUCCAGUGAUAGACAGGCUUUACCUCUCAUCUCACAG AGGCGUUAUCGCUGACAAUCAAGCAAAAUGGGCUGUC CCGACAACACGGACAGAUGACAAGUUGCGAAUGGAGA CAUGCUUCCAGCAGGCGUGUAAGGGUAAAAUCCAAGC ACUUUGCGAGAAUCCCGAGUGGACACCAUUGAAGGAU AACAGGAUUCCUUCAUACGGGGUCUUGUCUGUUGAUC UGAGUCUGACAGUUGAGCUUAAAAUCAAAAUUGUUU CAGGAUUCGGGCCAUUGAUCACACACGGUUCAGGGAU GGACCUAUACAAAUCCAACCACAACAAUAUGUAUUGG CUGACUAUCCCGCCAAUGAAGAACCUGGCCUUAGGUG UAAUCAACACAUUGGAGUGGAUACCGAGAUUCAAGG UUAGUCCCAACCUCUUCACUGUUCCAAUUAAGGAAGC AGGCGAGGACUGCCAUGCCCCAACAUACCUACCUGCG GAGGUGGAUGGUGAUGUCAAACUCAGUUCCAAUCUG GUGAUUCUACCUGGUCAAGAUCUCCAAUAUGUUCUGG CAACCUACGAUACUUCCAGAGUUGAACAUGCUGUAGU UUAUUACGUUUACAGCCCAAGCCGCUCAUUUUCUUAC UUUUAUCCUUUUAGGUUGCCUGUAAGGGGGGUCCCCA UUGAAUUACAAGUGGAAUGCUUCACAUGGGACCAAA AACUCUGGUGCCGUCACUUCUGUGUGCUUGCGGACUC AGAAUCUGGUGGACAUAUCACUCACUCUGGGAUGGU GGGCAUGGGAGUCAGCUGCACAGCCACUCGGGAAGAU GGAACCAGCCGCAGAUAG	79
GC_H_MEASLES_D8 mRNA Sequence (assumes T100 tail)	G*GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAA UAUAAGAGCCACCAUGUCACCACAACGAGACCGGAUA AAUGCCUUCUACAAAGACAACCCCCAUCCUAAGGGAA	80

TABLE 13-continued

Description	Sequence	SEQ ID NO:
Sequence Length: 2126	GUAGGAUAGUUAUUAACAGAGAACAUCUUAUGAUUG AUAGACCUUAUGUUUUGCUGGCUGUUCUAUUCGUCA UGUUUCUGAGCUUGAUCGGGUUGCUAGCCAUUGCAG GCAUUAGACUUCAUCGGGCAGCCAUCUACACCGCAGA GAUCCAUAAAAGCCUCAGCACCAAUCUGGAUGUAACU AACUCAAUCGAGCAUCAGGUUAAGGACGUGCUGACAC CACUCUUCAAGAUCAUCGGUGAUGAAGUGGGCUUGA GGACACCUCAGAGAUUCACUGACCUAGUGAAGUUCAU CUCUGACAAGAUUAAAUUCCUUAAUCCGGACAGGGAA UACGACUUCAGAGAUCUCACUUGGUGUAUCAACCCGC CAGAGAGAAUCAAAUUGGAUUAUGAUCAAUACUGUG CAGAUGUGGCUGCUGAAGAACUCAUGAAUGCAUUGG UGAACUCAACUCUACUGGAGACCAGGGCAACCAAUCA GUUCCUAGCUGUCUCAAAGGGAAACUGCUCAGGGCCC ACUACAAUCAGAGGCCAAUUCUCAAACAUGUCGCUGU CCCUGUUGGACUUGUAUUUAAGUCGAGGUUACAAUG UGUCAUCUAUAGUCACUAUGACAUCCCAGGGAAUGUA CGGGGGAACUUACCUAGUGGAAAAGCCUAAUCUGAGC AGCAAAGGGUCAGAGUUGUCACAACUGAGCAUGCACC GAGUGUUUGAAGUAGGUGUUAUCAGAAAUCCGGGUU UGGGGGCUCCGGUAUUCCAUAUGACAAACUAUCUUGA GCAACCAGUCAGUAAUGAUUUCAGCAACUGCAUGGUG GCUUUGGGGGAGCUCAAGUUCGCAGCCCUCUGUCACA GGGAAGAUUCUAUCACAAUUCCCUAUCAGGGAUCAGG GAAAGGUGUCAGCUUCCAGCUUGUCAAGCUAGGUGUC UGGAAAUCCCCAACCGACAUGCAAUCCUGGGUCCCCC UAUCAACGGAUGAUCCAGUGAUAGACAGGCUUUACCU CUCAUCUCACAGAGGCGUUAUCGCUGACAAUCAAGCA AAAUGGGCUGUCCCGACAACACGGACAGAUGACAAGU UGCGAAUGGAGACAUGCUUCCAGCAGGCGUGUAAGG GUAAAAUCCAAGCACUUUGCGAGAAUCCCGAGUGGAC ACCAUUGAAGGAUAACAGGAUUCCUUCAUACGGGGUC UUGUCUGUUGAUCUGAGUCUGACAGUUGAGCUUAAA AUCAAAAUUGUUUCAGGAUUCGGGCCAUUGAUCACAC ACGGUUCAGGGAUGGACCUAUACAAAUCCAACCACAA CAAUAUGUAUUGGCUGACUAUCCCGCCAAUGAAGAAC CUGGCCUUAGGUGUAAUCAACACAUUGGAGUGGAUA CCGAGAUUCAAGGUUAGUCCCAACCUCUUCACUGUUC CAAUUAAGGAAGCAGGCGAGGACUGCCAUGCCCCAAC AUACCUACCUGCGGAGGUGGAUGGUGAUGUCAAACUC AGUUCCAAUCUGGUGAUUCUACCUGGUCAAGAUCUCC AAUAUGUUCUGGCAACCUACGAUACUUCCAGAGUUGA ACAUGCUGUAGUUUAUUACGUUUACAGCCCAAGCCGC UCAUUUUCUUACUUUUAUCCUUUUAGGUUGCCUGUA AGGGGGGUCCCCAUUGAAUUACAAGUGGAAUGCUUC ACAUGGGACCAAAAACUCUGGUGCCGUCACUUCUGUG UGCUUGCGGACUCAGAAUCUGGUGGACAUAUCACUCA CUCUGGGAUGGUGGGCAUGGGAGUCAGCUGCACAGCC ACUCGGGAAGAUGGAACCAGCCGCAGAUAGUGAUAA UAGGCUGGAGCCUCGGUGGCCAAGCUUCUUGCCCCUU GGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACCCG UACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG CAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAUCUAG	

TABLE 14

MeV Amino Acid Sequences

Description	Sequence	SEQ ID NO:
GC_F_MEASLES_B3.1 ORF Sequence, AA	MGLKVNVSAVFMAVLLTLQTPAGQIHWGNLSKIGVVG IGSASYKVMTRSSHQSLVIKLMPNITLLNNCTRVEIA EYRRLLRTVLEPIRDALNAMTQNIRPVQSVASSRRHK RFAGVVLAGAALGVATAAQITAGIALHRSMLNSQAID NLRASLETTNQAIEAIRQAGQEMILAVQGVQDYINNE LIPSMNQLSCDLIGQKLGLKLLRYYTEILSLFGPSLR DPISAEISIQALSYALGGDINKVLEKLGYSGGDLLGI LESRGIKARITHVDTESYFIVLSIAYPTLSEIKGVIV HRLEGVSYNIGSQEWYTTVPKYVATQGYLISNFDESS CTFMPEGTVCSQNALYPMSPLLQECLRGSTKSCARTL VSGSFGNRFILSQGNLIANCASILCKCYTTGTIINQD	47

TABLE 14-continued

MeV Amino Acid Sequences

Description	Sequence	SEQ ID NO:
	PDKILTYIAADRCPVVEVNGVTIQVGSRRYPDAVYLH RIDLGPPISLERLDVGTNLGNAIAKLEDAKELLESSD QILRSMKGLSSTSIVYILIAVCLGGLIGIPTLICCCR GRCNKKGEQVGMSRPGLKPDLTGTSKSYVRSL*	
GC_F_MEASLES_D8 ORF Sequence, AA	MGLKVNVSVIFMAVLLTLQTPTGQIHWGNLSKIGVVG VGSASYKVMTRSSHQSLVIKLMPNITLLNNCTRVGIA EYRRLLRTVLEPIRDALNAMTQNIRPVQSVASSRRHK RFAGVVLAGAALGVATAAQITAGIALHQSMLNSQAID NLRASLETTNQAIEAIRQAGQEMILAVQGVQDYINNE LIPSMNQLSCDLIGQKLGLKLLRYYTEILSLFGPSLR DPISAEISIQALSYALGGDINKVLEKLGYSGGDLLGI LESRGIKARITHVDTESYFIVLSIAYPTLSEIKGVIV HRLEGVSYNIGSQEWYTTVPKYVATQGYLISNFDESS CTFMPEGTVCSQNALYPMSPLLQECLRGSTKSCARTL VSGSFGNRFILSQGNLIANCASILCKCYTTGTIINQD PDKILTYIAADHCPVVEVNGVTIQVGSRRYPDAVYLH RIDLGPPISLERLDVGTNLGNAIAKLEDAKELLESSD QILRSMKGLSSTSIVYILIAVCLGGLIGIPALICCCR GRCNKKGEQVGMSRPGLKPDLTGTSKSYVRSL*	48
GC_H_MEASLES_B3 ORF Sequence, AA	MSPQRDRINAFYKDNPYPKGSRIVINREHLMIDRPYV LLAVLFVMFLSLIGLLAIAGIRLHRAAIYTAEIHKSL STNLDVTNSIEHQVKDVLTPLFKIIGDEVGLRTPQRF TDLVKFISDKIKFLNPDREYDFRDLTWCINPPERIKL DYDQYCADVAAEELMNALVNSTLLETRTTTQFLAVSK GNCSGPTTIRGQFSNMSLSLLDLYLGRGYNVSSIVTM TSQGMYGGTYLVEKPNLNSKGSELSQLSMYRVFEVGV IRNPGLGAPVFHMTNYFEQPVSNGLGNCMVALGELKL AALCHGDDSIIIPYQGSGKGVSFQLVKLGVWKSPTDM QSWVPLSTDDPVVDRLYLSSHRGVIADNQAKWAVPTT RTDDKLRMETCFQQACKGKIQALCENPEWVPLKDNRI PSYGVLSVDLSLTVELKIKIASGFGPLITHGSGMDLY KSNCNNVYWLTIPPMRNLALGVINTLEWIPRFKVSPN LFTVPIKEAGEDCHAPTYLPAEVDGDVKLSSNLVILP GQDLQYVLATYDTSRVEHAVVYYVYSPSRSFSYFYPF RLPIKGVPIELQVECFTWDQKLWCRHFCVLADSESGG LITHSGMVGMGVSCTATREDGTNRR*	49
GC_H_MEASLES_D8 ORF Sequence, AA	MSPQRDRINAFYKDNPHPKGSRIVINREHLMIDRPYV LLAVLFVMFLSLIGLLAIAGIRLHRAAIYTAEIHKSL STNLDVTNSIEHQVKDVLTPLFKIIGDEVGLRTPQRF TDLVKFISDKIKFLNPDREYDFRDLTWCINPPERIKL DYDQYCADVAAEELMNALVNSTLLETRATNQFLAVSK GNCSGPTTIRGQFSNMSLSLLDLYLSRGYNVSSIVTM TSQGMYGGTYLVEKPNLSSKGSELSQLSMHRVFEVGV IRNPGLGAPVFHMTNYLEQPVSNDFSNCMVALGELKF AALCHREDSITIPYQGSGKGVSFQLVKLGVWKSPTDM QSWVPLSTDDPVIDRLYLSSHRGVIADNQAKWAVPTT RTDDKLRMETCFQQACKGKIQALCENPEWTPLKDNRI PSYGVLSVDLSLTVELKIKIVSGFGPLITHGSGMDLY KSNHNNMYWLTIPPMKNLALGVINTLEWIPRFKVSPN LFTVPIKEAGEDCHAPTYLPAEVDGDVKLSSNLVILP GQDLQYVLATYDTSRVEHAVVYYVYSPSRSFSYFYPF RLPVRGVPIELQVECFTWDQKLWCRHFCVLADSESGG HITHSGMVGMGVSCTATREDGTSRR*	50

TABLE 15

MeV NCBI Accession Numbers (Amino Acid Sequences)

Type	Virus Name	GenBank Accession
hemagglutinin	hemagglutinin [Measles virus strain Moraten]	AAF85673.1
hemagglutinin	hemagglutinin [Measles virus strain Rubeovax]	AAF85689.1
hemagglutinin	hemagglutinin [Measles virus]	AAF89824.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAA91369.1
hemagglutinin	hemagglutinin [Measles virus]	BAJ23068.1
hemagglutinin	hemagglutinin protein [Measles virus]	BAB39848.1
hemagglutinin	hemagglutinin [Measles virus]	AAA50551.1
hemagglutinin	RecName: Full = Hemagglutinin glycoprotein	P08362.1
hemagglutinin	hemagglutinin [Measles virus]	AAB63802.1

TABLE 15-continued

MeV NCBI Accession Numbers (Amino Acid Sequences)

Type	Virus Name	GenBank Accession
hemagglutinin	hemagglutinin [Measles virus]	AAA56650.1
hemagglutinin	hemagglutinin [Measles virus]	AAA56642.1
hemagglutinin	hemagglutinin [Measles virus]	AAA74936.1
hemagglutinin	hemagglutinin protein [Measles virus]	BAH56665.1
hemagglutinin	hemagglutinin [Measles virus]	ACC86105.1
hemagglutinin	hemagglutinin [Measles virus strain Edmonston-Zagreb]	AAF85697.1
hemagglutinin	hemagglutinin [Measles virus]	AAR89413.1
hemagglutinin	hemagglutinin [Measles virus]	AAA56653.1
hemagglutinin	RecName: Full = Hemagglutinin glycoprotein	P35971.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94916.1
hemagglutinin	hemagglutinin [Measles virus]	AAC03036.1
hemagglutinin	hemagglutinin [Measles virus]	AAF85681.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94927.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94925.1
hemagglutinin	hemagglutinin protein [Measles virus]	BAB39835.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94931.1
hemagglutinin	hemagglutinin [Measles virus genotype A]	AFO84712.1
hemagglutinin	hemagglutinin [Measles virus]	AAA56639.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94926.1
hemagglutinin	hemagglutinin protein [Measles virus]	BAB39836.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94929.1
hemagglutinin	RecName: Full = Hemagglutinin glycoprotein	P06830.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94928.1
hemagglutinin	hemagglutinin protein [Measles virus]	BAB39837.1
hemagglutinin	hemagglutinin [Measles virus]	AAA74935.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43780.1
hemagglutinin	hemagglutinin [Measles virus]	BAA09952.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43815.1
hemagglutinin	hemagglutinin [Measles virus]	AAF28390.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94923.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43785.1
hemagglutinin	hemagglutinin [Measles virus]	ABD34001.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43782.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43781.1
hemagglutinin	hemagglutinin [Measles virus]	BAH22353.1
hemagglutinin	hemagglutinin [Measles virus]	AAC35878.2
hemagglutinin	hemagglutinin protein [Measles virus]	AAL86996.1
hemagglutinin	hemagglutinin [Measles virus]	CAA76066.2
hemagglutinin	hemagglutinin [Measles virus]	AAA46428.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43803.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94918.1
hemagglutinin	hemagglutinin [Measles virus]	AAF72162.1
hemagglutinin	hemagglutinin [Measles virus]	AAM70154.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43776.1
hemagglutinin	hemagglutinin [Measles virus genotype D4]	ACT78395.1
hemagglutinin	hemagglutinin [Measles virus genotype D7]	AAL02030.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43789.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43774.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94920.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94922.1
hemagglutinin	hemagglutinin [Measles virus]	ABB59491.1
hemagglutinin	hemagglutinin protein [Measles virus]	BAB39843.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43804.1
hemagglutinin	hemagglutinin [Measles virus]	AAX52048.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94930.1
hemagglutinin	hemagglutinin [Measles virus]	AAA74526.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43814.1
hemagglutinin	hemagglutinin [Measles virus]	ABB59493.1
hemagglutinin	hemagglutinin [Measles virus genotype D4]	AAL02019.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94919.1
hemagglutinin	hemagglutinin protein [Measles virus]	AAL86997.1
hemagglutinin	hemagglutinin [Measles virus genotype C2]	AAL02017.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43769.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43808.1
hemagglutinin	hemagglutinin [Measles virus]	BAO97032.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43805.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43777.1
hemagglutinin	hemagglutinin [Measles virus]	AAL67793.1
hemagglutinin	hemagglutinin [Measles virus]	AAF89816.1
hemagglutinin	hemagglutinin [Measles virus genotype D4]	AAL02020.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43786.1
hemagglutinin	hemagglutinin protein [Measles virus strain MVi/New Jersey.USA/45.05]	AEP40452.1
hemagglutinin	hemagglutinin [Measles virus]	AAA74531.1
hemagglutinin	hemagglutinin [Measles virus]	AAB63800.1
hemagglutinin	hemagglutinin [Measles virus]	AAO21711.1

TABLE 15-continued

MeV NCBI Accession Numbers (Amino Acid Sequences)

Type	Virus Name	GenBank Accession
hemagglutinin	hemagglutinin [Measles virus genotype D8]	ALE27189.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43810.1
hemagglutinin	hemagglutinin [Measles virus]	AAF89817.1
hemagglutinin	hemagglutinin [Measles virus genotype D6]	AAL02022.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43800.1
hemagglutinin	hemagglutinin protein [Measles virus genotype B3]	AGA17219.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43770.1
hemagglutinin	hemagglutinin protein [Measles virus strain MVi/Texas.USA/4.07]	AEP40444.1
hemagglutinin	hemagglutinin [Measles virus]	AAX52047.1
hemagglutinin	hemagglutinin [Measles virus]	AAB63794.1
hemagglutinin	hemagglutinin [Measles virus]	AAB63796.1
hemagglutinin	hemagglutinin [Measles virus]	AAA74528.1
hemagglutinin	hemagglutinin [Measles virus]	AAB63774.1
hemagglutinin	hemagglutinin [Measles virus]	AAB63795.1
hemagglutinin	hemagglutinin [Measles virus]	AAA74519.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAB43778.1
fusion protein	fusion protein [Measles virus strain Moraten]	AAF85672.1
fasion protein	fusion protein [Measles virus]	AAA56645.1
fusion protein	fusion protein [Measles virus strain Rubeovax]	AAF85688.1
fusion protein	fusion protein [Measles virus]	AAF85680.1
fusion protein	fusion protein [Measles virus]	AEF30359.1
fusion protein	fusion protein [Measles virus]	BAA09957.1
fusion protein	fusion protein [Measles virus]	AAV84957.1
fusion protein	fusion protein [Measles virus MeV-eGFP__Edm-tag]	AII16636.1
fusion protein	fusion protein [Measles virus]	ABY58018.1
fusion protein	fusion protein [Measles virus]	BAA19838.1
fusion protein	fusion protein [Measles virus]	AAA56641.1
fusion protein	F protein [Measles virus]	ABK40529.1
fusion protein	fusion protein [Measles virus]	AAA56652.1
fusion protein	fusion protein [Measles virus]	ABY58017.1
fusion protein	fusion protein [Measles virus]	ABB71645.1
fusion protein	fusion protein [Measles virus]	NP__056922.1
fusion protein	fusion protein [Measles virus strain AIK-C]	AAF85664.1
fusion protein	fusion protein [Measles virus]	BAB60865.1
fusion protein	fusion protein [Measles virus]	BAA09950.1
fusion protein	fusion protein [Measles virus strain MVi/New York.USA/26.09/3]	AEP40403.1
fusion protein	fusion protein [Measles virus]	AAA74934.1
fusion protein	fusion protein [Measles virus]	CAB38075.1
fusion protein	fusion protein [Measles virus strain MVi/Texas.USA/4.07]	AEP40443.1
fusion protein	fusion protein [Measles virus]	AAF02695.1
fusion protein	fusion protein [Measles virus]	AAF02696.1
fusion protein	fusion protein [Measles virus]	AAT99301.1
fusion protein	fusion protein [Measles virus]	ABB71661.1
fusion protein	fusion protein [Measles virus]	BAK08874.1
fusion protein	fusion protein [Measles virus]	AAF02697.1
fusion protein	fusion protein [Measles virus genotype D4]	AFY12704.1
fusion protein	fusion protein [Measles virus strain MVi/California.USA/16.03]	AEP40467.1
fusion protein	fusion protein [Measles virus genotype D8]	AHN07989.1
fusion protein	fusion protein [Measles virus]	AAA46421.1
fusion protein	fusion protein [Measles virus]	AAA56638.1
fusion protein	fusion protein [Measles virus strain MVi/Virginia.USA/15.09]	AEP40419.1
fusion protein	fusion protein [Measles virus genotype D8]	ALE27200.1
fusion protein	fusion protein [Measles virus genotype D8]	AFY12695.1
fusion protein	fusion protein [Measles virus genotype D8]	ALE27248.1
fusion protein	fusion protein [Measles virus genotype D8]	ALE27224.1
fusion protein	fusion protein [Measles virus]	AAT99300.1
fusion protein	fusion protein [Measles virus]	BAH96592.1
fusion protein	fusion protein [Measles virus strain MVi/California.USA/8.04]	AEP40459.1
fusion protein	fusion protein [Measles virus genotype D8]	AIG94081.1
fusion protein	fusion protein [Measles virus]	BAA09951.1
fusion protein	fusion protein [Measles virus genotype D8]	ALE27194.1
fusion protein	fusion protein [Measles virus]	BAA33871.1
fusion protein	fusion protein [Measles virus strain MVi/Washington.USA/18.08/1]	AEP40427.1
fusion protein	fusion protein [Measles virus]	ABY21182.1
fusion protein	fusion protein [Measles virus genotype D8]	ALE27284.1
fusion protein	fusion protein [Measles virus]	ACA09725.1
fusion protein	fusion protein [Measles virus genotype D8]	ALE27314.1
fusion protein	fusion protein [Measles virus genotype G3]	AFY12712.1
fusion protein	fusion protein [Measles virus genotype D8]	ALE27368.1

TABLE 15-continued

MeV NCBI Accession Numbers (Amino Acid Sequences)

Type	Virus Name	GenBank Accession
fusion protein	RecName: Full = Fusion glycoprotein F0; Contains: RecName: Full = Fusion glycoprotein F2; Contains: RecName: Full = Fusion glycoprotein F1; Flags: Precursor	P35973.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53713.1
	unnamed protein product [Measles virus]	CAA34588.1
fusion protein	fusion protein [Measles virus]	CAA76888.1
fusion protein	fusion protein [Measles virus genotype B3.1]	AIY55563.1
fusion protein	fusion protein [Measles virus]	ADO17330.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53703.1
fusion protein	fusion protein [Measles virus genotype B3]	AGA17208.1
fusion protein	fusion protein [Measles virus]	AAL29688.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53706.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53701.1
fusion protein	fusion protein [Measles virus genotype B3]	ALE27092.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53714.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53694.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53668.1
fusion protein	fusion protein [Measles virus]	ACC86094.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53670.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53707.1
fusion protein	fusion protein [Measles virus genotype B3]	AGA17216.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53671.1
fusion protein	fusion protein [Measles virus strain MVi/New Jersey.USA/45.05]	AEP40451.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53684.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53688.1
fusion protein	fusion protein [Measles virus genotype B3]	AGA17214.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53683.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53667.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53686.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53685.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53681.1
	unnamed protein product [Measles virus]	CAA34589.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53678.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53710.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53669.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53664.1
fusion protein	fusion protein [Measles virus]	AAA50547.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53679.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53709.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53672.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53697.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53689.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53676.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53675.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53663.1
fusion protein	fusion protein [Measles virus]	BAA19841.1
fusion protein	fusion protein [Measles virus]	AAF02701.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53680.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53674.1
C protein	C protein [Measles virus strain Moraten]	AAF85670.1
C protein	RecName: Full = Protein C	P03424.1
C protein	C protein [Measles virus]	ACN54404.1
C protein	C protein [Measles virus]	ACN54412.1
C protein	RecName: Full = Protein C	P35977.1
C protein	C protein [Measles virus]	AAF85678.1
C protein	C protein [Measles virus]	ABD33998.1
C protein	unnamed protein product [Measles virus]	CAA34586.1
C protein	C protein [Measles virus]	BAJ51786.1
C protein	C protein [Measles virus]	BAA33869.1
C protein	virulence factor [Measles virus]	ABO69700.1
C protein	C protein [Measles virus]	NP_056920.1
C protein	C protein [Measles virus]	ADO17333.1
C protein	C protein [Measles virus]	ACC86082.1
C protein	C protein [Measles virus]	BAA33875.1
C protein	C protein [Measles virus]	ABY21189.1
C protein	C protein [Measles virus]	BAE98296.1
C protein	C protein [Measles virus]	ADU17782.1
C protein	C protein [Measles virus strain MVi/Virginia.USA/15.09]	AEP40417.1
C protein	C protein [Measles virus]	ADU17814.1
C protein	C protein [Measles virus]	ADU17798.1
C protein	C protein [Measles virus genotype D4]	AFY12700.1
C protein	C protein [Measles virus]	ADU17784.1
C protein	C protein [Measles virus strain MVi/California.USA/16.03]	AEP40465.1

TABLE 15-continued

MeV NCBI Accession Numbers (Amino Acid Sequences)

Type	Virus Name	GenBank Accession
C protein	C protein [Measles virus]	ABB71643.1
C protein	C protein [Measles virus]	AEI91027.1
C protein	C protein [Measles virus]	ADU17874.1
C protein	C protein [Measles virus]	ADU17903.1
C protein	C protein [Measles virus]	CAA34579.1
C protein	C protein [Measles virus]	ADU17790.1
C protein	C protein [Measles virus]	ADU17800.1
C protein	C protein [Measles virus]	ABB71667.1
C protein	unnamed protein product [Measles virus]	CAA34572.1
C protein	C protein [Measles virus strain MVi/Arizona.USA/11.08/2]	AEP40433.1
C protein	C protein [Measles virus]	ADU17830.1
C protein	C protein [Measles virus]	ADU17947.1
C protein	C protein [Measles virus]	ADU17818.1
C protein	C protein [Measles virus strain MVi/New Jersey.USA/45.05]	AEP40449.1
C protein	C protein [Measles virus strain MVi/Texas.USA/4.07]	AEP40441.1
C protein	C protein [Measles virus]	ADU17864.1
C protein	C protein [Measles virus]	ADU17838.1
C protein	C protein [Measles virus]	ADU17881.1
C protein	C protein [Measles virus strain MVi/Washington.USA/18.08/1]	AEP40425.1
C protein	C protein [Measles virus]	ADU17927.1
C protein	C protein [Measles virus]	ADU17953.1
C protein	C protein [Measles virus]	ADU17889.1
C protein	C protein [Measles virus]	ADU17963.1
C protein	C protein [Measles virus]	ADU17893.1
C protein	C protein [Measles virus]	ADU17820.1
C protein	C protein [Measles virus]	ABB71651.1
C protein	C protein [Measles virus]	ADU17786.1
C protein	C protein [Measles virus]	ADU17862.1
C protein	C protein [Measles virus]	ADU17923.1
C protein	C protein [Measles virus]	ADU17959.1
C protein	C protein [Measles virus]	ADU17951.1
C protein	C protein [Measles virus]	ADU17916.1
C protein	C protein [Measles virus]	ADU17957.1
C protein	C protein [Measles virus]	ADU17925.1
C protein	C protein [Measles virus]	ADU17901.1
C protein	C protein [Measles virus]	ADU17887.1
C protein	C protein [Measles virus]	ADU17832.1
C protein	C protein [Measles virus]	ADU17891.1
C protein	C protein [Measles virus]	ADU17961.1
C protein	C protein [Measles virus]	ADU17872.1
C protein	C protein [Measles virus]	ADU17929.1
C protein	C protein [Measles virus]	ADU17908.1
C protein	C protein [Measles virus]	ADU17910.1
C protein	C protein [Measles virus]	ADU17921.1
C protein	C protein [Measles virus]	ADU17824.1
C protein	C protein [Measles virus strain MVi/Pennsylvania.USA/20.09]	AEP40473.1
C protein	C protein [Measles virus]	ADU17828.1
C protein	C protein [Measles virus]	ADU17812.1
C protein	C protein [Measles virus genotype D8]	AFY12692.1
C protein	nonstructural C protein [Measles virus]	ABA59559.1
C protein	RecName: Full = Protein C	Q00794.1
C protein	nonstructural C protein [Measles virus]	ADO17934.1
C protein	nonstructural C protein [Measles virus]	ACJ66773.1
C protein	C protein [Measles virus genotype G3]	AFY12708.1
C protein	RecName: Full = Protein C	P26035.1
C protein	C protein [Measles virus]	BAA84128.1
nucleoprotein	RecName: Full = Nucleoprotein; AltName: Full = Nucleocapsid protein; Short = NP; Short = Protein N	Q77M43.1
nucleoprotein	nucleocapsid protein [Measles virus strain Rubeovax]	AAF85683.1
nucleoprotein	RecName: Full = Nucleoprotein; AltName: Full = Nucleocapsid protein; Short = NP; Short = Protein N	Q89933.1
nucleoprotein	nucleocapsid protein [Measles virus strain AIK-C]	AAF85659.1
nucleoprotein	nucleoprotein [Measles virus]	ABI54102.1
nucleoprotein	nucleoprotein [Measles virus]	AAA56643.1
nucleoprotein	nucleoprotein [Measles virus]	AAC03050.1
nucleoprotein	nucleoprotein [Measles virus]	AAA18990.1

TABLE 15-continued

MeV NCBI Accession Numbers (Amino Acid Sequences)

Type	Virus Name	GenBank Accession
nucleoprotein	nucleoprotein [Measles virus]	AAA56640.1
nucleoprotein	RecName: Full = Nucleoprotein; AltName: Full = Nucleocapsid protein; Short = NP; Short = Protein N	P35972.1
nucleoprotein	RecName: Full=Nucleoprotein; AltName: Full = Nucleocapsid protein; Short = NP; Short = Protein N	P10050.1
nucleoprotein	N protein [Measles virus]	BAB60956.1
nucleoprotein	RecName: Full = Nucleoprotein; AltName: Full = Nucleocapsid protein; Short = NP; Short = Protein N	B1AAA7.1
nucleoprotein	nucleoprotein [Measles virus]	AAA18991.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46894.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46871.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46872.1
nucleoprotein	nucleoprotein [Measles virus]	ABU49606.1
nucleoprotein	nucleocapsid protein [Measles virus]	AAA75494.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46883.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46892.1
nucleoprotein	unnamed protein product [Measles virus]	CAA34584.1
nucleoprotein	nucleoprotein [Measles virus]	AAA18997.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46863.1
nucleoprotein	nucleoprotein [Measles virus]	AEF30352.1
nucleoprotein	nucleoprotein [Measles virus]	ABI54103.1
nucleoprotein	nucleocapsid protein [Measles virus]	AAA46433.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46902.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46873.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46906.1
nucleoprotein	nucleoprotein [Measles virus]	AAA74547.1
nucleoprotein	nucleoprotein [Measles virus]	AAA74537.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46862.1
nucleoprotein	nucleocapsid protein [Measles virus]	BAA09961.1
nucleoprotein	nucleoprotein [Measles virus]	AAO15875.1
nucleoprotein	nucleoprotein [Measles virus]	AAO15871.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46882.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60124.1
nucleoprotein	nucleoprotein [Measles virus]	ABI54104.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46869.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46880.1
nucleoprotein	nucleoprotein [Measles virus]	AAA74541.1
nucleoprotein	nucleocapsid protein [Measles virus strain MVi/New Jersey.USA/45.05]	AEP40446.1
nucleoprotein	nucleoprotein [Measles virus]	ABI54110.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46903.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46899.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46901.1
nucleoprotein	nucleocapsid protein [Measles virus]	ABB71640.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60113.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60114.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60116.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46895.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60121.1
nucleoprotein	nucleoprotein [Measles virus]	ABI54111.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46889.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46898.1
nucleoprotein	nucleoprotein [Measles virus genotype B3]	ALE27083.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60118.1
nucleoprotein	nucleocapsid protein [Measles virus]	CAA34570.1
nucleoprotein	nucleoprotein [Measles virus]	AAC29443.1
nucleoprotein	nucleocapsid protein [Measles virus strain MVi/Washington.USA/18.08/1]	AEP40422.1
nucleoprotein	nucleoprotein [Measles virus]	AAO15872.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46874.1
nucleoprotein	nucleoprotein [Measles virus]	AAA74550.1
nucleoprotein	nucleocapsid protein [Measles virus]	ABB71648.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46900.1
nucleoprotein	nucleoprotein [Measles virus]	BAH22440.1
nucleoprotein	nucleocapsid protein [Measles virus]	AAA46432.1
nucleoprotein	nucleocapsid protein [Measles virus]	BAA33867.1
nucleoprotein	nucleoprotein [Measles virus]	AAA74539.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60115.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60123.1
nucleoprotein	nucleocapsid protein [Measles virus]	ABB71664.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60125.1
nucleoprotein	nucleoprotein [Measles virus]	AAA74546.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46886.1

TABLE 15-continued

MeV NCBI Accession Numbers (Amino Acid Sequences)

Type	Virus Name	GenBank Accession
nucleoprotein	nucleoprotein [Measles virus]	BAH22350.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46867.1
nucleoprotein	nucleocapsid protein [Measles virus]	BAA09954.1
nucleoprotein	nucleoprotein [Measles virus]	AAO15873.1
nucleoprotein	nucleocapsid protein [Measles virus]	AEP95735.1
nucleoprotein	nucleoprotein [Measles virus]	AAL37726.1
nucleoprotein	nucleoprotein [Measles virus]	AAA74549.1
nucleoprotein	RecName: Full = Nucleoprotein; AltName: Full = Nucleocapsid protein; Short = NP; Short = Protein N	P26030.1
nucleoprotein	nucleoprotein [Measles virus ETH55/99]	AAK07777.1
nucleoprotein	nucleoprotein [Measles virus genotype B3]	AGA17238.1
nucleoprotein	nucleoprotein [Measles virus]	AEF30351.1
nucleoprotein	nucleoprotein [Measles virus genotype B3]	AGA17242.1
nucleoprotein	nucleoprotein [Measles virus ETH54/98]	AAK07776.1
nucleoprotein	nucleoprotein [Measles virus]	AAA74548.1
nucleoprotein	nucleoprotein [Measles virus]	AAA19221.1
nucleoprotein	nucleoprotein [Measles virus]	AAC03039.1
nucleoprotein	nucleoprotein [Measles virus]	AAA19223.1
nucleoprotein	nucleoprotein [Measles virus genotype B3]	AGA17241.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60122.1
nucleoprotein	nucleoprotein [Measles virus]	CAC34599.1
nucleoprotein	nucleoprotein [Measles virus]	AAC03042.1
nucleoprotein	nucleoprotein [Measles virus]	CAC34604.1
nucleoprotein	nucleoprotein [Measles virus]	AAA74544.1
nucleoprotein	nucleocapsid protein [Measles virus]	NP_056918.1
V Protein	RecName: Full = Non-structural protein V	Q9IC37.1
V Protein	RecName: Full = Non-structural protein V	Q9EMA9.1
V Protein	V protein [Measles virus]	ACN54411.1
V Protein	V protein [Measles virus]	ACN54403.1
V Protein	V protein [Measles virus]	AEP95742.1
V Protein	V protein [Measles virus strain MVi/Virginia.USA/15.09]	AEP40416.1
V Protein	V protein [Measles virus]	ADU17801.1
V Protein	V protein [Measles virus]	ADU17849.1
V Protein	V protein [Measles virus]	ABB71642.1
V Protein	V protein [Measles virus genotype D8]	AFY12693.1
V Protein	V protein [Measles virus]	YP_003873249.2
V Protein	V protein [Measles virus strain MVi/Arizona.USA/11.08/2]	AEP40432.1
V Protein	RecName: Full = Non-structural protein V	P26036.1
V Protein	V protein [Measles virus strain MVi/California.USA/16.03]	AEP40464.1
V Protein	V protein [Measles virus strain MVi/California.USA/8.04]	AEP40456.1
V Protein	V protein [Measles virus]	ABY21188.1
V Protein	V protein [Measles virus strain MVi/Washington.USA/18.08/1]	AEP40424.1
V Protein	V protein [Measles virus]	BAH96581.1
V Protein	V protein [Measles virus]	ABB71666.1
V Protein	RecName: Full = Non-structural protein V	P60168.1
V Protein	V protein [Measles virus]	BAH96589.1
V Protein	V protein [Measles virus]	ADU17954.1
V Protein	V protein [Measles virus strain MVi/New York.USA/26.09/3]	AEP40400.1
V Protein	V protein [Measles virus]	ABY21196.1
V Protein	virulence factor [Measles virus]	ABO69701.1
V Protein	V protein [Measles virus]	ABB71650.1
V Protein	V protein [Measles virus]	ACC86086.1
V Protein	V protein [Measles virus genotype D4]	AFY12702.1
V Protein	V protein [Measles virus strain MVi/New Jersey.USA/45.05]	AEP40448.1
V Protein	V protein [Measles virus]	BAE98295.1
V Protein	V protein [Measles virus]	ACC86083.1
V Protein	V protein [Measles virus]	ACU5139.1
V Protein	V protein [Measles virus]	ADO17334.1
V Protein	V protein [Measles virus]	ADU17930.1
V Protein	V protein [Measles virus genotype G3]	AFY12710.1
V Protein	V protein [Measles virus strain MVi/Pennsylvania.USA/20.09]	AEP40472.1
V Protein	phosphoprotein [Measles virus]	ADU17839.1
V Protein	V protein [Measles virus]	ADU17894.1
V Protein	V protein [Measles virus]	ACN50010.1

TABLE 15-continued

MeV NCBI Accession Numbers (Amino Acid Sequences)

Type	Virus Name	GenBank Accession
V Protein	V protein [Measles virus]	ADU17892.1
	unnamed protein product [Measles virus]	CAA34585.1
V Protein	V protein [Measles virus]	ABD33997.1

TABLE 16

Name	Sequence	SEQ ID NO:
	Flagellin Nucleic Acid Sequences	
NT (5' UTR, ORF, 3' UTR)	TCAAGCTTTTGGACCCTCGTACAGAAGCTAATACGACTCACTAT AGGGAAATAAGAGAGAAAAGAAGAGTAAGAAGAAATATAAG AGCCACCATGGCACAAGTCATTAATACAAACAGCCTGTCGCTG TTGACCCAGAATAACCTGAACAAATCCCAGTCCGCACTGGGCA CTGCTATCGAGCGTTTGTCTTCCGGTCTGCGTATCAACAGCGCG AAAGACGATGCGGCAGGACAGGCGATTGCTAACCGTTTTACCG CGAACATCAAAGGTCTGACTCAGGCTTCCCGTAACGCTAACGA CGGTATCTCCATTGCGCAGACCACTGAAGGCGCGCTGAACGAA ATCAACAACAACCTGCAGCGTGTGCGTGAACTGGCGGTTCAGT CTGCGAATGGTACTAACTCCCAGTCTGACCTCGACTCCATCCAG GCTGAAATCACCCAGCGCCTGAACGAAATCGACCGTGTATCCG GCCAGACTCAGTTCAACGGCGTGAAAGTCCTGGCGCAGGACAA CACCCTGACCATCCAGGTTGGTGCCAACGACGGTGAAACTATC GATATTGATTTAAAAGAAATCAGCTCTAAAACACTGGGACTTG ATAAGCTTAATGTCCAAGATGCCTACACCCCGAAAGAAACTGC TGTAACCGTTGATAAAACTACCTATAAAAATGGTACAGATCCT ATTACAGCCCAGAGCAATACTGATATCCAAACTGCAATTGGCG GTGGTGCAACGGGGGTTACTGGGGCTGATATCAAATTTAAAGA TGGTCAATACTATTTAGATGTTAAAGGCGGTGCTTCTGCTGGTG TTTATAAAGCCACTTATGATGAAACTACAAAGAAAGTTAATAT TGATACGACTGATAAAACTCCGTTGGCAACTGCGGAAGCTACA GCTATTCGGGGAACGGCCACTATAACCCACAACCAAATTGCTG AAGTAACAAAAGAGGGTGTTGATACGACCACAGTTGCGGCTCA ACTTGCTGCAGCAGGGGTTACTGGCGCCGATAAGGACAATACT AGCCTTGTAAAACTATCGTTTGAGGATAAAAACGGTAAGGTTA TTGATGGTGGCTATGCAGTGAAAATGGGCGACGATTTCTATGC CGCTACATATGATGAGAAAACAGGTGCAATTACTGCTAAAACC ACTACTTATACAGATGGTACTGGCGTTGCTCAAACTGGAGCTGT GAAATTTGGTGGCGCAAATGGTAAATCTGAAGTTGTTACTGCT ACCGATGGTAAGACTTACTTAGCAAGCGACCTTGACAAACATA ACTTCAGAACAGGCGGTGAGCTTAAAGAGGTTAATACAGATAA GACTGAAAACCCACTGCAGAAAATTGATGCTGCCTTGGCACAG GTTGATACACTTCGTTCTGACCTGGGTGCGGTTCAGAACCGTTT CAACTCCGCTATCACCAACCTGGGCAATACCGTAAATAACCTG TCTTCTGCCCGTAGCCGTATCGAAGATTCCGACTACGCAACCGA AGTCTCCAACATGTCTCGCGCGCAGATTCTGCAGCAGGCCGGT ACCTCCGTTCTGGCGCAGGCGAACCAGGTTCCGCAAAACGTCC TCTCTTTACTGCGTTGATAATAGGCTGGAGCCTCGGTGGCCATG CTTCTTGCCCCTTGGGCCTCCCCCCAGCCCCTCCTCCCCTTCCTG CACCCGTACCCCCGTGGTCTTTGAATAAAGTCTGAGTGGGCGG C	51
ORF Sequence, NT	ATGGCACAAGTCATTAATACAAACAGCCTGTCGCTGTTGACCC AGAATAACCTGAACAAATCCCAGTCCGCACTGGGCACTGCTAT CGAGCGTTTGTCTTCCGGTCTGCGTATCAACAGCGCGAAAGAC GATGCGGCAGGACAGGCGATTGCTAACCGTTTTACCGCGAACA TCAAAGGTCTGACTCAGGCTTCCCGTAACGCTAACGACGGTAT CTCCATTGCGCAGACCACTGAAGGCGCGCTGAACGAAATCAAC AACAACCTGCAGCGTGTGCGTGAACTGGCGGTTCAGTCTGCGA ATGGTACTAACTCCCAGTCTGACCTCGACTCCATCCAGGCTGAA ATCACCCAGCGCCTGAACGAAATCGACCGTGTATCCGGCCAGA CTCAGTTCAACGGCGTGAAAGTCCTGGCGCAGGACAACACCCT GACCATCCAGGTTGGTGCCAACGACGGTGAAACTATCGATATT GATTTAAAAGAAATCAGCTCTAAAACACTGGGACTTGATAAGC TTAATGTCCAAGATGCCTACACCCCGAAAGAAACTGCTGTAAC CGTTGATAAAACTACCTATAAAAATGGTACAGATCCTATTACA GCCCAGAGCAATACTGATATCCAAACTGCAATTGGCGGTGGTG CAACGGGGGTTACTGGGGCTGATATCAAATTTAAAGATGGTCA ATACTATTTAGATGTTAAAGGCGGTGCTTCTGCTGGTGTTTATA AAGCCACTTATGATGAAACTACAAAGAAAGTTAATATTGATAC GACTGATAAAACTCCGTTGGCAACTGCGGAAGCTACAGCTATT CGGGGAACGGCCACTATAACCCACAACCAAATTGCTGAAGTAA	52

TABLE 16-continued

Name	Sequence	SEQ ID NO:
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	TGCAGCAGGGGTTACTGGCGCCGATAAGGACAATACTAGCCTT	
	GTAAAACTATCGTTTGAGGATAAAAACGGTAAGGTTATTGATG	
	GTGGCTATGCAGTGAAAATGGGCGACGATTTCTATGCCGCTAC	
	ATATGATGAGAAAACAGGTGCAATTACTGCTAAAACCACTACT	
	TATACAGATGGTACTGGCGTTGCTCAAACTGGAGCTGTGAAAT	
	TTGGTGGCGCAAATGGTAAATCTGAAGTTGTTACTGCTACCGAT	
	GGTAAGACTTACTTAGCAAGCGACCTTGACAAACATAACTTCA	
	GAACAGGCGGTGAGCTTAAAGAGGTTAATACAGATAAGACTG	
	AAAACCCACTGCAGAAAATTGATGCTGCCTTGGCACAGGTTGA	
	TACACTTCGTTCTGACCTGGGTGCGGTTCAGAACCGTTTCAACT	
	CCGCTATCACCAACCTGGGCAATACCGTAAATAACCTGTCTTCT	
	GCCCGTAGCCGTATCGAAGATTCCGACTACGCAACCGAAGTCT	
	CCAACATGTCTCGCGCGCAGATTCTGCAGCAGGCCGGTACCTC	
	CGTTCTGGCGCAGGCGAACCAGGTTCCGCAAAACGTCCTCTCTT	
	TACTGCGT	
mRNA Sequence (assumes T100 tail)	G*GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUAA	53
	GAGCCACCAUGGCACAAGUCAUUAAUACAAACAGCCUGUCGC	
	UGUUGACCCAGAAUAACCUGAACAAAUCCCAGUCCGCACUGG	
	GCACUGCUAUCGAGCGUUUGUCUUCCGGUCUGCGUAUCAACA	
	GCGCGAAAGACGAUGCGGCAGGACAGGCGAUUGCUAACCGUU	
	UUACCGCGAACAUCAAAGGUCUGACUCAGGCUUCCCGUAACG	
	CUAACGACGGUAUCUCCAUUGCGCAGACCACUGAAGGCGCGC	
	UGAACGAAAUCAACAACAACCUGCAGCGUGUGCGUGAACUGG	
	CGGUUCAGUCUGCGAAUGGUACUAACUCCCAGUCUGACCUCG	
	ACUCCAUCCAGGCUGAAAUCACCCAGCGCCUGAACGAAAUCG	
	ACCGUGUAUCCGGCCAGACUCAGUUCAACGGCGUGAAAGUCC	
	UGGCGCAGGACAACACCCUGACCAUCCAGGUUGGUGCCAACG	
	ACGGUGAAACUAUCGAUAUUGAUUUAAAAGAAAUCAGCUCU	
	AAAACACUGGGACUUGAUAAGCUUAAUGUCCAAGAUGCCUAC	
	ACCCCGAAAGAAACUGCUGUAACCGUUGAUAAAACUACCUAU	
	AAAAAUGGUACAGAUCCUAUUACAGCCCAGAGCAAUACUGAU	
	AUCCAAACUGCAAUUGGCGGUGGUGCAACGGGGGUUACUGG	
	GGCUGAUAUCAAAUUUAAAGAUGGUCAAUACUAUUUAGAUG	
	UUAAAGGCGGUGCUUCUGCUGGUGUUUAUAAAGCCACUUAU	
	GAUGAAACUACAAAGAAAGUUAAUAUUGAUACGACUGAUAA	
	AACUCCGUUGGCAACUGCGGAAGCUACAGCUAUUCGGGGAAC	
	GGCCACUAUAACCCACAACCAAAUUGCUGAAGUAACAAAAGA	
	GGGUGUUGAUACGACCACAGUUGCGGCUCAACUUGCUGCAGC	
	AGGGGUUACUGGCGCCGAUAAGGACAAUACUAGCCUUGUAA	
	AACUAUCGUUUGAGGAUAAAAACGGUAAGGUUAUUGAUGGU	
	GGCUAUGCAGUGAAAAUGGGCGACGAUUUCUAUGCCGCUACA	
	UAUGAUGAGAAAACAGGUGCAAUUACUGCUAAAACCACUAC	
	UUAUACAGAUGGUACUGGCGUUGCUCAAACUGGAGCUGUGA	
	AAUUUGGUGGCGCAAAUGGUAAAUCUGAAGUUGUUACUGCU	
	ACCGAUGGUAAGACUUACUUAGCAAGCGACCUUGACAAACAU	
	AACUUCAGAACAGGCGGUGAGCUUAAAGAGGUUAAUACAGA	
	UAAGACUGAAAACCCACUGCAGAAAAUUGAUGCUGCCUUGGC	
	ACAGGUUGAUACACUUCGUUCUGACCUGGGUGCGGUUCAGAA	
	CCGUUUCAACUCCGCUAUCACCAACCUGGGCAAUACCGUAAA	
	UAACCUGUCUUCUGCCCGUAGCCGUAUCGAAGAUUCCGACUA	
	CGCAACCGAAGUCUCCAACAUGUCUCGCGCGCAGAUUCUGCA	
	GCAGGCCGGUACCUCCGUUCUGGCGCAGGCGAACCAGGUUCC	
	GCAAAACGUCCUCUCUUUACUGCGUUGAUAAUAGGCUGGAGC	
	CUCGGUGGCCAUGCUUCUUGCCCCUUGGGCCUCCCCCCAGCC	
	CCUCCUCCCCUUCCUGCACCCGUACCCCCGUGGUCUUUGAAU	
	AAAGUCUGAGUGGGCGGCAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAUCUAG	

Flagellin mRNA Sequences

NT (5' UTR, ORF, 3' UTR)	UCAAGCUUUUGGACCCUCGUACAGAAGCUAAUACGACUCACU	81
	AUAGGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA	
	AGAGCCACCAUGGCACAAGUCAUUAAUACAAACAGCCUGUCG	
	CUGUUGACCCAGAAUAACCUGAACAAAUCCCAGUCCGCACUG	
	GGCACUGCUAUCGAGCGUUUGUCUUCCGGUCUGCGUAUCAAC	
	AGCGCGAAAGACGAUGCGGCAGGACAGGCGAUUGCUAACCGU	
	UUUACCGCGAACAUCAAAGGUCUGACUCAGGCUUCCCGUAAC	
	GCUAACGACGGUAUCUCCAUUGCGCAGACCACUGAAGGCGCG	
	CUGAACGAAAUCAACAACAACCUGCAGCGUGUGCGUGAACUG	
	GCGGUUCAGUCUGCGAAUGGUACUAACUCCCAGUCUGACCUC	
	GACUCCAUCCAGGCUGAAAUCACCCAGCGCCUGAACGAAAUC	
	GACCGUGUAUCCGGCCAGACUCAGUUCAACGGCGUGAAAGUC	
	CUGGCGCAGGACAACACCCUGACCAUCCAGGUUGGUGCCAAC	
	GACGGUGAAACUAUCGAUAUUGAUUUAAAAGAAAUCAGCUC	

TABLE 16-continued

Name	Sequence	SEQ ID NO:
	UAAAACACUGGGACUUGAUAAGCUUAAUGUCCAAGAUGCCU	
	ACACCCCGAAAGAAACUGCUGUAACCGUUGAUAAAACUACCU	
	AUAAAAAUGGGUACAGAUCCUAUUACAGCCCAGAGCAAUACUG	
	AUAUCCAAACUGCAAUUGGCGGUGGUGCAACGGGGGUUACU	
	GGGGCUGAUAUCAAAUUUAAAGAUGGUCAAUACUAUUUAGA	
	UGUUAAAGGCGGUGCUUCUGCUGGUGUUUAUAAAGCCACUU	
	AUGAUGAAACUACAAAGAAAGUUAAUAUUGAUACGACUGAU	
	AAAACUCCGUUGGCAACUGCGGAAGCUACAGCUAUUCGGGGA	
	ACGGCCACUAUAACCCACAACCAAAUUGCUGAAGUAACAAAA	
	GAGGGUGUUGAUACGACCACAGUUGCGGCUCAACUUGCUGCA	
	GCAGGGGUUACUGGCGCCGAUAAGGACAAUACUAGCCUUGUA	
	AAACUAUCGUUUGAGGAUAAAAACGGUAAGGUUAUUGAUGG	
	UGGCUAUGCAGUGAAAAUGGGCGACGAUUUCUAUGCCGCUAC	
	AUAUGAUGAGAAAACAGGUGCAAUUACUGCUAAAACCACUA	
	CUUAUACAGAUGGUACUGGCGUUGCUCAAACUGGAGCUGUG	
	AAAUUUGGUGGCGCAAAUGGUAAAUCUGAAGUUGUUACUGC	
	UACCGAUGGUAAGACUUACUUAGCAAGCGACCUUGACAAACA	
	UAACUUCAGAACAGGCGGUGAGCUUAAAGAGGUUAAUACAG	
	AUAAGACUGAAAACCCACUGCAGAAAAUUGAUGCUGCCUUGG	
	CACAGGUUGAUACACUUCGUUCUGACCUGGGUGCGGUUCAGA	
	ACCGUUUCAACUCCGCUAUCACCAACCUGGGCAAUACCGUAA	
	AUAACCUGUCUUCUGCCCGUAGCCGUAUCGAAGAUUCCGACU	
	ACGCAACCGAAGUCUCCAACAUGUCUCGCGCGCAGAUUCUGC	
	AGCAGGCCGGUACCUCCGUUCUGGCGCAGGCGAACCAGGUUC	
	CGCAAAACGUCCUCUCUUUACUGCGUUGAUAAUAGGCUGGAG	
	CCUCGGUGGCCAUGCUUCUUGCCCCUUGGGCCUCCCCCCAGC	
	CCCUCCUCCCCUUCCUGCACCCGUACCCCCGUGGUCUUUGAA	
	UAAAGUCUGAGUGGGCGGC	
ORF Sequence, NT	AUGGCACAAGUCAUUAAUACAAACAGCCUGUCGCUGUUGACC	82
	CAGAAUAACCUGAACAAAUCCCAGUCCGCACUGGGCACUGCU	
	AUCGAGCGUUUGUCUUCCGGUCUGCGUAUCAACAGCGCGAAA	
	GACGAUGCGGCAGGACAGGCGAUUGCUAACCGUUUUACCGCG	
	AACAUCAAAGGUCUGACUCAGGCUUCCCGUAACGCUAACGAC	
	GGUAUCUCCAUUGCGCAGACCACUGAAGGCGCGCUGAACGAA	
	AUCAACAACAACCUGCAGCGUGUGCGUGAACUGGCGGUUCAG	
	UCUGCGAAUGGUACUAACUCCCAGUCUGACCUCGACUCCAUC	
	CAGGCUGAAAUCACCCAGCGCCUGAACGAAAUCGACCGUGUA	
	UCCGGCCAGACUCAGUUCAACGGCGUGAAAGUCCUGGCGCAG	
	GACAACACCCUGACCAUCCAGGUUGGUGCCAACGACGGUGAA	
	ACUAUCGAUAUUGAUUUAAAAGAAAUCAGCUCUAAAACACU	
	GGGACUUGAUAAGCUUAAUGUCCAAGAUGCCUACACCCCGAA	
	AGAAACUGCUGUAACCGUUGAUAAAACUACCUAUAAAAAUG	
	GUACAGAUCCUAUUACAGCCCAGAGCAAUACUGAUAUCCAAA	
	CUGCAAUUGGCGGUGGUGCAACGGGGGUUACUGGGGCUGAU	
	AUCAAAUUUAAAGAUGGUCAAUACUAUUUAGAUGUUAAAGG	
	CGGUGCUUCUGCUGGUGUUUAUAAAGCCACUUAUGAUGAAA	
	CUACAAAGAAAGUUAAUAUUGAUACGACUGAUAAAACUCCG	
	UUGGCAACUGCGGAAGCUACAGCUAUUCGGGGAACGGCCACU	
	AUAACCCACAACCAAAUUGCUGAAGUAACAAAAGAGGGUGU	
	UGAUACGACCACAGUUGCGGCUCAACUUGCUGCAGCAGGGGU	
	UACUGGCGCCGAUAAGGACAAUACUAGCCUUGUAAAACUAUC	
	GUUUGAGGAUAAAAACGGUAAGGUUAUUGAUGGUGGCUAUG	
	CAGUGAAAAUGGGCGACGAUUUCUAUGCCGCUACAUAUGAU	
	GAGAAAACAGGUGCAAUUACUGCUAAAACCACUACUUAUACA	
	GAUGGUACUGGCGUUGCUCAAACUGGAGCUGUGAAAUUUGG	
	UGGCGCAAAUGGUAAAUCUGAAGUUGUUACUGCUACCGAUG	
	GUAAGACUUACUUAGCAAGCGACCUUGACAAACAUAACUUCA	
	GAACAGGCGGUGAGCUUAAAGAGGUUAAUACAGAUAAGACU	
	GAAAACCCACUGCAGAAAAUUGAUGCUGCCUUGGCACAGGUU	
	GAUACACUUCGUUCUGACCUGGGUGCGGUUCAGAACCGUUUC	
	AACUCCGCUAUCACCAACCUGGGCAAUACCGUAAAUAACCUG	
	UCUUCUGCCCGUAGCCGUAUCGAAGAUUCCGACUACGCAACC	
	GAAGUCUCCAACAUGUCUCGCGCGCAGAUUCUGCAGCAGGCC	
	GGUACCUCCGUUCUGGCGCAGGCGAACCAGGUUCCGCAAAAC	
	GUCCUCUCUUUACUGCGU	
mRNA Sequence (assumes T100 tail)	G*GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUAA	83
	GAGCCACCAUGGCACAAGUCAUUAAUACAAACAGCCUGUCGC	
	UGUUGACCCAGAAUAACCUGAACAAAUCCCAGUCCGCACUGG	
	GCACUGCUAUCGAGCGUUUGUCUUCCGGUCUGCGUAUCAACA	
	GCGCGAAAGACGAUGCGGCAGGACAGGCGAUUGCUAACCGUU	
	UUACCGCGAACAUCAAAGGUCUGACUCAGGCUUCCCGUAACG	
	CUAACGACGGUAUCUCCAUUGCGCAGACCACUGAAGGCGCGC	
	UGAACGAAAUCAACAACAACCUGCAGCGUGUGCGUGAACUGG	
	CGGUUCAGUCUGCGAAUGGUACUAACUCCCAGUCUGACCUCG	
	ACUCCAUCCAGGCUGAAAUCACCCAGCGCCUGAACGAAAUCG	

TABLE 16-continued

Name	Sequence	SEQ ID NO:
	ACCGUGUAUCCGGCCAGACUCAGUUCAACGGCGUGAAAGUCC	
	UGGCGCAGGACAACACCCUGACCAUCCAGGUUGGUGCCAACG	
	ACGGUGAAACUAUCGAUAUUGAUUUAAAAGAAAUCAGCUCU	
	AAAACACUGGGACUUGAUAAGCUUAAUGUCCAAGAUGCCUAC	
	ACCCCGAAAGAAACUGCUGUAACCGUUGAUAAAACUACCUAU	
	AAAAAUGGUACAGAUCCUAUUACAGCCCAGAGCAAUACUGAU	
	AUCCAAACUGCAAUUGGCGGUGGUGCAACGGGGGUUACUGG	
	GGCUGAUAUCAAAUUUAAAGAUGGUCAAUACUAUUUAGAUG	
	UUAAAGGCGGUGCUUCUGCUGGUGUUUAUAAAGCCACUUAU	
	GAUGAAACUACAAAGAAAGUUAAUAUUGAUACGACUGAUAA	
	AACUCCGUUGGCAACUGCGGAAGCUACAGCUAUUCGGGGAAC	
	GGCCACUAUAACCCACAACCAAAUUGCUGAAGUAACAAAAGA	
	GGGUGUUGAUACGACCACAGUUGCGGCUCAACUUGCUGCAGC	
	AGGGGUUACUGGCGCCGAUAAGGACAAUACUAGCCUUGUAA	
	AACUAUCGUUUGAGGAUAAAAACGGUAAGGUUAUUGAUGGU	
	GGCUAUGCAGUGAAAAUGGGCGACGAUUUCUAUGCCGCUACA	
	UAUGAUGAGAAAACAGGUGCAAUUACUGCUAAAACCACUAC	
	UUAUACAGAUGGUACUGGCGUUGCUCAAACUGGAGCUGUGA	
	AAUUUGGUGGCGCAAAUGGUAAAUCUGAAGUUGUUACUGCU	
	ACCGAUGGUAAGACUUACUUAGCAAGCGACCUUGACAAACAU	
	AACUUCAGAACAGGCGGUGAGCUUAAAGAGGUUAAUACAGA	
	UAAGACUGAAAACCCACUGCAGAAAAUUGAUGCUGCCUUGGC	
	ACAGGUUGAUACACUUCGUUCUGACCUGGGUGCGGUUCAGAA	
	CCGUUUCAACUCCGCUAUCACCAACCUGGGCAAUACCGUAAA	
	UAACCUGUCUUCUGCCCGUAGCCGUAUCGAAGAUUCCGACUA	
	CGCAACCGAAGUCUCCAACAUGUCUCGCGCGCAGAUUCUGCA	
	GCAGGCCGGUACCUCCGUUCUGGCGCAGGCGAACCAGGUUCC	
	GCAAAACGUCCUCUCUUUACUGCGUUGAUAAUAGGCUGGAGC	
	CUCGGUGGCCAUGCUUCUUGCCCCUUGGGCCUCCCCCCAGCC	
	CCUCCUCCCCUUCCUGCACCCGUACCCCCGUGGUCUUUGAAU	
	AAAGUCUGAGUGGGCGGCAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAUCUAG	

TABLE 17

Flagellin Amino Acid Sequences

Name	Sequence	SEQ ID NO:
ORF Sequence, AA	MAQVINTNSLSLLTQNNLNKSQSALGTAIERLSSGLRINSAKDDAA GQAIANRFTANIKGLTQASRNANDGISIAQTTEGALNEINNNLQRV RELAVQSANGTNSQSDLDSIQAEITQRLNEIDRVSGQTQFNGVKVL AQDNTLTIQVGANDGETIDIDLKEISSKTLGLDKLNVQDAYTPKET AVTVDKTTYKNGTDPITAQSNTDIQTAIGGGATGVTGADIKFKDGQ YYLDVKGGASAGVYKATYDETTKKVNIDTTDKTPLATAEATAIRGT ATITHNQIAEVTKEGVDTTTVAAQLAAAGVTGADKDNTSLVKLSFE DKNGKVIDGGYAVKMGDDFYAATYDEKTGAITAKTTTYTDGTGVAQ TGAVKFGGANGKSEVVTATDGKTYLASDLDKHNFRTGGELKEVNTD KTENPLQKIDAALAQVDTLRSDLGAVQNRFNSAITNLGNTVNNLSS ARSRIEDSDYATEVSNMSRAQILQQAGTSVLAQANQVPQNVLSLLR	54
Flagellin-GS linker-circumsporozoite protein (CSP)	MAQVINTNSLSLLTQNNLNKSQSALGTAIERLSSGLRINSAKDDAA GQAIANRFTANIKGLTQASRNANDGISIAQTTEGALNEINNNLQRV RELAVQSANSTNSQSDLDSIQAEITQRLNEIDRVSGQTQFNGVKVL AQDNTLTIQVGANDGETIDIDLKQINSQTLGLDTLNVQQKYKVSDT AATVTGYADTTIALDNSTFKASATGLGGTDQKIDGDLKFDDTTGKY YAKVTVTGGTGKDGYYEVSVDKTNGEVTLAGGATSPLTGGLPATAT EDVKNVQVANADLTEAKAALTAAGVTGTASVVKMSYTDNNGKTIDG GLAVKVGDDYYSATQNKDGSISINTTKYTADDGTSKTALNKLGGAD GKTEVVSIGGKTYAASKAEGHNFKAQPDLAEAAATTTENPLQKIDA ALAQVDTLRSDLGAVQNRFNSAITNLGNTVNNLTSARSRIEDSDYA TEVSNMSRAQILQQAGTSVLAQANQVPQNVLSLLRGGGGSGGGGSM MAPDPNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPN ANPNANPNANPNANPNANPNANPNANPNANPNKNNQGNGQGH NMPNDPNRNVDENANANNAVKNNNNEEPSDKHIEQYLKKIKNSIST EWSPCSVTCGNGIQVRIKPGSANKPKDELDYENDIEKKICKMEKCS SVFNVVNS	55
Flagellin-RPVT linker-	MMAPDPNANPNANPNANPNANPNANPNANPNANPNANPNANP NANPNANPNANPNANPNANPNANPNANPNANPNANPNKNNQGNGQG HNMPNDPNRNVDENANANNAVKNNNNEEPSDKHIEQYLKKIKNSIS	56

TABLE 17-continued

Flagellin Amino Acid Sequences

Name	Sequence	SEQ ID NO:
circumsporozoite protein (CSP)	TEWSPCSVTCGNGIQVRIKPGSANKPKDELDYENDIEKKICKMEKC SSVFNVVNSRPVTMAQVINTNSLSLLTQNNLNKSQSALGTAIERLS SGLRINSAKDDAAGQAIANRFTANIKGLTQASRNANDGISIAQTTE GALNEINNNLQRVRELAVQSANSTNSQSDLDSIQAEITQRLNEIDR VSGQTQFNGVKVLAQDNTLTIQVGANDGETIDIDLKQINSQTLGLD TLNVQQKYKVSDTAATVTGYADTTIALDNSTFKASATGLGGTDQKI DGDLKFDDTTGKYYAKVTVTGGTGKDGYYEVSVDKTNGEVTLAGGA TSPLTGGLPATATEDVKNVQVANADLTEAKAALTAAGVTGTASVVK MSYTDNNGKTIDGGLAVKVGDDYYSATQNKDGSISINTTKYTADDG TSKTALNKLGGADGKTEVVSIGGKTYAASKAEGHNFKAQPDLAEAA ATTTENPLQKIDAALAQVDTLRSDLGAVQNRFNSAITNLGNTVNNL TSARSRIEDSDYATEVSNMSRAQILQQAGTSVLAQANQVPQNVLSL LR	

TABLE 18

Human Metapneumovirus Mutant Amino Acid Sequences

Strain	Sequence	SEQ ID NO:
HMPV_SC_DSCAV1_4MMV	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLE VGDVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGS FVLGAIALGVAAAAAVTAGVAICKTIRLESEVTAINNALKKTNEAVSTLGN GVRVLAFAVRELKDFVSKNLTRALNKNKCDIDDLKMAVSFSQFNRRFLNVV RQFSDNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKG FGILCGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLRED QGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTT NYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCS YITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVA LDQVFENIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSI FIIIKKTKKPTGAPPELSGVTNNGFIPHN	85
HMPV_SC_DSTRIC_4MMV	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLE VGDVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGS FVLGAIALGVAAAAAVTAGVAICKTIRLESEVTAINNALKKTNEAVSTLGN GVRVLATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVV RQFSDNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKG FGILCGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLRED QGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTT NYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCS YITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEHQWHVA LDQVFENIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSI FIIIKKTKKPTGAPPELSGVTNNGFIPHN	86
HMPV_SC_DM_Krarup_T74LD185P	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLE VGDVENLTCSDGPSLIKTELDLLKSALRELKTVSADQLAREEQIENPGSGS FVLGAIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGN GVRVLATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVV RQFSDNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKG FGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLRED QGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTT NYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCS YITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVA LDQVFENIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSI FIIIKKTKKPTGAPPELSGVTNNGFIPHN	87
HMPV_SC_TM_Krarup_T74LD185PD454N	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLE VGDVENLTCSDGPSLIKTELDLLKSALRELKTVSADQLAREEQIENPGSGS FVLGAIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGN GVRVLATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVV RQFSDNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKG FGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLRED QGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTT NYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCS YITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPENQFQVA LDQVFENIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSI FIIIKKTKKPTGAPPELSGVTNNGFIPHN	88
HMPV_SC_4M_Krarup_T74LS170LD185P	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLE VGDVENLTCSDGPSLIKTELDLLKSALRELKTVSADQLAREEQIENPGSGS FVLGAIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGN	89

TABLE 18-continued

Human Metapneumovirus Mutant Amino Acid Sequences

Strain	Sequence	SEQ ID NO:
	GVRVLATAVRELKDFVLKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVV RQFSDNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKG FGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLRED QGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTT NYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCS YITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVA LDQVFENIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSI FIIIKKTKKPTGAPPELSGVTNNGFIPHN	
HMPV_SC_5M_Krarup_T74LS170LD185PD454N	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLE VGDVENLTCSDGPSLIKTELDLLKSALRELKTVSADQLAREEQIENPGSGS FVLGAIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGN GVRVLATAVRELKDFVLKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVV RQFSDNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKG FGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLRED QGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTT NYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCS YITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPENQFQVA LDQVFENIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSI FIIIKKTKKPTGAPPELSGVTNNGFIPHN	90
HMPV_SC_DM_Krarup_E51PT74L	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLP VGDVENLTCSDGPSLIKTELDLLKSALRELKTVSADQLAREEQIENPGSGS FVLGAIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGN GVRVLATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVV RQFSDNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKG FGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLRED QGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTT NYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCS YITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVA LDQVFENIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSI FIIIKKTKKPTGAPPELSGVTNNGFIPHN	91
HMPV_SC_TM_Krarup_E51PT74LD454N	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLP VGDVENLTCSDGPSLIKTELDLLKSALRELKTVSADQLAREEQIENPGSGS FVLGAIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGN GVRVLATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVV RQFSDNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKG FGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLRED QGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTT NYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCS YITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPENQFQVA LDQVFENIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSI FIIIKKTKKPTGAPPELSGVTNNGFIPHN	92
HMPV_SC_StabilizeAlpha_T74L	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLE VGDVENLTCSDGPSLIKTELDLLKSALRELKTVSADQLAREEQIENPGSGS FVLGAIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGN GVRVLATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVV RQFSDNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKG FGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLRED QGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTT NYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCS YITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVA LDQVFENIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSI FIIIKKTKKPTGAPPELSGVTNNGFIPHN	93
HMPV_SC_StabilizeAlpha_V55L	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLE VGDLENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGS FVLGAIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGN GVRVLATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVV RQFSDNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKG FGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLRED QGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTT NYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCS YITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVA LDQVFENIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSI FIIIKKTKKPTGAPPELSGVTNNGFIPHN	94
HMPV_SC_StabilizeAlpha_S170L	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLE VGDVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGS FVLGAIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGN GVRVLATAVRELKDFVLKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVV RQFSDNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKG FGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLRED	95

TABLE 18-continued

Human Metapneumovirus Mutant Amino Acid Sequences

Strain	Sequence	SEQ ID NO:
	QGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTT NYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCS YITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVA LDQVFENIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSI FIIIKKTKKPTGAPPELSGVTNNGFIPHN	
HMPV_SC_StabilizeAlpha_T174W	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLE VGDVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGS FVLGAIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGN GVRVLATAVRELKDFVSKNLWRAINKNKCDIDDLKMAVSFSQFNRRFLNVV RQFSDNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKG FGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLRED QGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTT NYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCS YITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVA LDQVFENIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSI FIIIKKTKKPTGAPPELSGVTNNGFIPHN	96
HMPV_SC_4M_Stabilize-Alpha_V55LT74LS170LT174W	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLE VGDLENLTCSDGPSLIKTELDLLKSALRELKTVSADQLAREEQIENPGSGS FVLGAIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGN GVRVLATAVRELKDFVLKNLWRAINKNKCDIDDLKMAVSFSQFNRRFLNVV RQFSDNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKG FGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLRED QGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTT NYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCS YITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVA LDQVFENIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSI FIIIKKTKKPTGAPPELSGVTNNGFIPHN	97
HMPV_ProlineStab_E51P	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLP VGDVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGS FVLGAIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGN GVRVLATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVV RQFSDNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKG FGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLRED QGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTT NYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCS YITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVA LDQVFENIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSI FIIIKKTKKPTGAPPELSGVTNNGFIPHN	98
HMPV_ProlineStab_D185P	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLE VGDVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGS FVLGAIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGN GVRVLATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVV RQFSDNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKG FGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLRED QGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTT NYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCS YITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVA LDQVFENIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSI FIIIKKTKKPTGAPPELSGVTNNGFIPHN	99
HMPV_ProlineStab_D183P	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLE VGDVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGS FVLGAIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGN GVRVLATAVRELKDFVSKNLTRAINKNKCPIDDLKMAVSFSQFNRRFLNVV RQFSDNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKG FGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLRED QGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTT NYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCS YITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVA LDQVFENIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSI FIIIKKTKKPTGAPPELSGVTNNGFIPHN	100
HMPV_ProlineStab_E131P	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLE VGDVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGS FVLGAIALGVAAAAAVTAGVAIAKTIRLPSEVTAINNALKKTNEAVSTLGN GVRVLATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVV RQFSDNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKG FGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLRED QGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTT NYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCS YITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVA	101

TABLE 18-continued

Human Metapneumovirus Mutant Amino Acid Sequences

Strain	Sequence	SEQ ID NO:
	LDQVFENIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSI FIIIKKTKKPTGAPPELSGVTNNGFIPHN	
HMPV_ProlineStab_D447P	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLE VGDVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGS FVLGAIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGN GVRVLATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVV RQFSDNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKG FGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLRED QGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTT NYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCS YITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFPPIKFPEDQFQVA LDQVFENIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSI FIIIKKTKKPTGAPPELSGVTNNGFIPHN	102
HMPV_TrimerRepulsionD454N	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLE VGDVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGS FVLGAIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGN GVRVLATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVV RQFSDNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKG FGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLRED QGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTT NYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCS YITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPENQFQVA LDQVFENIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSI FIIIKKTKKPTGAPPELSGVTNNGFIPHN	103
HMPV_TrimerRepulsionE453N	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLE VGDVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGS FVLGAIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGN GVRVLATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVV RQFSDNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKG FGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLRED QGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTT NYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCS YITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPQDQFQVA LDQVFENIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSI FIIIKKTKKPTGAPPELSGVTNNGFIPHN	104
HMPV_StabilizeAlphaF196W	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLE VGDVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGS FVLGAIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGN GVRVLATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQWNRRFLNVV RQFSDNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKG FGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLRED QGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTT NYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCS YITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVA LDQVFENIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSI FIIIKKTKKPTGAPPELSGVTNNGFIPHN	105

TABLE 19

Strain	Nucleic Acid Sequence	SEQ ID NO:
Human Metapneumovirus Mutant Nucleic Acid Sequences		
HMPV_SC_DSCAV1_4MMV	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG CAGGCGTGGCCATCTGCAAGACCATCAGACTGGAAAGCG AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC CTTTGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC CTGACACGGGCCCTGAACAAGAACAAGTGCGACATCGAC	106

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
	GACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGC	
	GGTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGG	
	AATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCT	
	GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG	
	GCCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCG	
	ACGGAAAGGCTTCGGCATTCTGTGTGGCGTGTACGGCAGC	
	AGCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGA	
	TCGACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTG	
	TAGCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGA	
	GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG	
	TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGAC	
	CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG	
	AGCAGAGCAAAGAGTGCAACATCAACATCAGCACCACCA	
	ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC	
	TATGGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTT	
	ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG	
	GCATCATCAAGCAGCTGAACAAGGGCTGCAGCTACATCAC	
	CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG	
	TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC	
	AAGGGCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGT	
	TCCCTGAGGATCAGTTCAACGTGGCCCTGGACCAGGTGTT	
	CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC	
	AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC	
	TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC	
	CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC	
	AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG	
	ACCAACAATGGCTTCATCCCTCACAAC	
HMPV_SC_DSTRIC_4MMV	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	107
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG	
	AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA	
	ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA	
	GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG	
	CAGGCGTGGCCATCTGCAAGACCATCAGACTGGAAAGCG	
	AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG	
	AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC	
	CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC	
	CTGACACGGGCCATTAACAAGAACAAGTGCGACATCGAC	
	GACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGC	
	GGTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGG	
	AATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCT	
	GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG	
	GCCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCG	
	ACGGAAAGGCTTCGGCATTCTGTGTGGCGTGTACGGCAGC	
	AGCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGA	
	TCGACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTG	
	TAGCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGA	
	GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG	
	TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGAC	
	CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG	
	AGCAGAGCAAAGAGTGCAACATCAACATCAGCACCACCA	
	ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC	
	TATGGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTT	
	ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG	
	GCATCATCAAGCAGCTGAACAAGGGCTGCAGCTACATCAC	
	CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG	
	TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC	
	AAGGGCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGT	
	TCCCTGAGCACCAGTGGCATGTGGCCCTGGACCAGGTGTT	
	CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC	
	AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC	
	TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC	
	CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC	
	AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG	
	ACCAACAATGGCTTCATCCCTCACAAC	
HMPV_SC_DM_Krarup_T74LD185P	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	108
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA	
	ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA	

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
	CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGAG	
	CCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAGC	
	AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCGA	
	AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA	
	GGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGCC	
	ACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAACC	
	TGACACGGGCCATTAACAAGAACAAGTGCGACATCCCTGA	
	CCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCGG	
	TTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGAA	
	TCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTGA	
	GCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGGC	
	CAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGAC	
	GGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCAG	
	CGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATCG	
	ACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTAG	
	CGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGGA	
	CCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTAC	
	TACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCAC	
	GTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAGC	
	AGAGCAAAGAGTGCAACATCAACATCAGCACCACCAACT	
	ATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT	
	GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA	
	AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT	
	CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC	
	CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC	
	AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG	
	GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC	
	TGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG	
	AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA	
	GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT	
	CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG	
	ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA	
	AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA	
	CAATGGCTTCATCCCTCACAAC	
HMPV_SC_TM_Krarup_T74LD185PD454N	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	109
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA	
	ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA	
	CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGAG	
	CCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAGC	
	AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCGA	
	AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA	
	GGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGCC	
	ACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAACC	
	TGACACGGGCCATTAACAAGAACAAGTGCGACATCCCTGA	
	CCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCGG	
	TTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGAA	
	TCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTGA	
	GCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGGC	
	CAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGAC	
	GGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCAG	
	CGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATCG	
	ACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTAG	
	CGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGGA	
	CCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTAC	
	TACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCAC	
	GTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAGC	
	AGAGCAAAGAGTGCAACATCAACATCAGCACCACCAACT	
	ATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT	
	GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA	
	AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT	
	CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC	
	CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC	
	AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG	
	GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC	
	TGAGAACCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG	
	AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA	
	GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT	
	CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG	
	ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA	
	AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA	
	CAATGGCTTCATCCCTCACAAC	

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
HMPV_SC_4M_Krarup_T74LS170LD185P	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGAG CCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAGC AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCGA AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA GGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGCC ACAGCCGTGCGCGAGCTGAAGGACTTCGTGCTTAAGAACC TGACACGGGCCATTAACAAGAACAAGTGCGACATCCCTGA CCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCGG TTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGAA TCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTGA GCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGGC CAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGAC GGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCAG CGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATCG ACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTAG CGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGGA CCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTAC TACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCAC GTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAGC AGAGCAAAGAGTGCAACATCAACATCAGCACCACCAACT ATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC TGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA CAATGGCTTCATCCCTCACAAC	110
HMPV_SC_5M_Krarup_T74LS170LD185PD454N	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGAG CCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAGC AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCGA AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA GGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGCC ACAGCCGTGCGCGAGCTGAAGGACTTCGTGCTTAAGAACC TGACACGGGCCATTAACAAGAACAAGTGCGACATCCCTGA CCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCGG TTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGAA TCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTGA GCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGGC CAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGAC GGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCAG CGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATCG ACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTAG CGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGGA CCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTAC TACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCAC GTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAGC AGAGCAAAGAGTGCAACATCAACATCAGCACCACCAACT ATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC TGAGAACCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG	111

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
	AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA CAATGGCTTCATCCCTCACAAC	
HMPV_SC_DM_Krarup_E51PT74L	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG AACCGGCTGGTACACCAACGTGTTCACACTGCCTGTGGGC GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGAG CCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAGC AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCGA AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA GGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGCC ACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAACC TGACACGGGCCATTAACAAGAACAAGTGCGACATCGACG ACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCG GTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGA ATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTG AGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGG CCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGA CGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCA GCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATC GACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTA GCGAGAAGAAGAGGCAATTACGCCTGCCTGCTGAGAGAGG ACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTA CTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCA CGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAG CAGAGCAAAGAGTGCAACATCAACATCAGCACCACCAAC TATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC TGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA CAATGGCTTCATCCCTCACAAC	112
HMPV_SC_TM_Krarup_E51PT74LD454N	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG AACCGGCTGGTACACCAACGTGTTCACACTGCCTGTGGGC GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGAG CCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAGC AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCGA AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA GGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGCC ACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAACC TGACACGGGCCATTAACAAGAACAAGTGCGACATCGACG ACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCG GTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGA ATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTG AGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGG CCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGA CGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCA GCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATC GACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTA GCGAGAAGAAGAGGCAATTACGCCTGCCTGCTGAGAGAGG ACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTA CTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCA CGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAG CAGAGCAAAGAGTGCAACATCAACATCAGCACCACCAAC TATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT	113

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT	
	CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC	
	CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC	
	AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG	
	GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC	
	TGAGAACCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG	
	AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA	
	GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT	
	CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG	
	ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA	
	AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA	
	CAATGGCTTCATCCCTCACAAC	
HMPV_SC_StabilizeAlpha_T74L	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	114
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA	
	ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA	
	CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGAG	
	CCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAGC	
	AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCGA	
	AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA	
	GGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGCC	
	ACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAACC	
	TGACACGGGCCATTAACAAGAACAAGTGCGACATCGACG	
	ACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCG	
	GTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGA	
	ATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTG	
	AGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGG	
	CCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGA	
	CGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCA	
	GCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATC	
	GACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTA	
	GCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGG	
	ACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTA	
	CTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCA	
	CGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAG	
	CAGAGCAAAGAGTGCAACATCAACATCAGCACCACCAAC	
	TATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT	
	GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA	
	AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT	
	CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC	
	CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC	
	AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG	
	GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC	
	TGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG	
	AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA	
	GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT	
	CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG	
	ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA	
	AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA	
	CAATGGCTTCATCCCTCACAAC	
HMPV_SC_StabilizeAlpha_V55L	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	115
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACCTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG	
	AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA	
	ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA	
	GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG	
	CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG	
	AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG	
	AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC	
	CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC	
	CTGACACGGGCCATTAACAAGAACAAGTGCGACATCGAC	
	GACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGC	
	GGTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGG	
	AATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCT	
	GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG	
	GCCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCG	
	ACGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGC	
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TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG	
	TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGAC	
	CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG	
	AGCAGAGCAAAGAGTGCAACATCAACATCAGCACCACCA	
	ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC	
	TATGGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTT	
	ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG	
	GCATCATCAAGCAGCTGAACAAGGGCTGCAGCTACATCAC	
	CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG	
	TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC	
	AAGGGCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGT	
	TCCCTGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTT	
	CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC	
	AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC	
	TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC	
	CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC	
	AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG	
	ACCAACAATGGCTTCATCCCTCACAAC	
HMPV_SC_StabilizeAlpha_S170L	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	116
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG	
	AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA	
	ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA	
	GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG	
	CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG	
	AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG	
	AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC	
	CACAGCCGTGCGCGAGCTGAAGGACTTCGTGCTTAAGAAC	
	CTGACACGGGCCATTAACAAGAACAAGTGCGACATCGAC	
	GACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGC	
	GGTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGG	
	AATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCT	
	GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG	
	GCCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCG	
	ACGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGC	
	AGCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGA	
	TCGACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTG	
	TAGCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGA	
	GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG	
	TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGAC	
	CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG	
	AGCAGAGCAAAGAGTGCAACATCAACATCAGCACCACCA	
	ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC	
	TATGGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTT	
	ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG	
	GCATCATCAAGCAGCTGAACAAGGGCTGCAGCTACATCAC	
	CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG	
	TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC	
	AAGGGCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGT	
	TCCCTGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTT	
	CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC	
	AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC	
	TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC	
	CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC	
	AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG	
	ACCAACAATGGCTTCATCCCTCACAAC	
HMPV_SC_StabilizeAlpha_T174W	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	117
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	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG	
	AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA	
	ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA	
	GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG	
	CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG	
	AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG	
	AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC	
	CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC	
	CTGTGGCGGGCCATTAACAAGAACAAGTGCGACATCGAC	

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG	
	GCCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCG	
	ACGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGC	
	AGCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGA	
	TCGACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTG	
	TAGCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGA	
	GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG	
	TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGAC	
	CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG	
	AGCAGAGCAAAGAGTGCAACATCAACATCAGCACCACCA	
	ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC	
	TATGGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTT	
	ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG	
	GCATCATCAAGCAGCTGAACAAGGGCTGCAGCTACATCAC	
	CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG	
	TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC	
	AAGGGCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGT	
	TCCCTGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTT	
	CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC	
	AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC	
	TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC	
	CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC	
	AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG	
	ACCAACAATGGCTTCATCCCTCACAAC	
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	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACCTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA	
	ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA	
	CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGAG	
	CCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAGC	
	AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCGA	
	AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA	
	GGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGCC	
	ACAGCCGTGCGCGAGCTGAAGGACTTCGTGCTTAAGAACC	
	TGTGGCGGGCCATTAACAAGAACAAGTGCGACATCGACG	
	ACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCG	
	GTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGA	
	ATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTG	
	AGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGG	
	CCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGA	
	CGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCA	
	GCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATC	
	GACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTA	
	GCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGG	
	ACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTA	
	CTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCA	
	CGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAG	
	CAGAGCAAAGAGTGCAACATCAACATCAGCACCACCAAC	
	TATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT	
	GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA	
	AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT	
	CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC	
	CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC	
	AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG	
	GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC	
	TGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG	
	AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA	
	GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT	
	CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG	
	ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA	
	AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA	
	CAATGGCTTCATCCCTCACAAC	
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	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGCCTGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
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TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG	
	AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC	
	CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC	
	CTGACACGGGCCATTAACAAGAACAAGTGCGACATCGAC	
	GACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGC	
	GGTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGG	
	AATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCT	
	GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG	
	GCCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCG	
	ACGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGC	
	AGCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGA	
	TCGACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTG	
	TAGCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGA	
	GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG	
	TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGAC	
	CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG	
	AGCAGAGCAAAGAGTGCAACATCAACATCAGCACCACCA	
	ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC	
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	ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG	
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	CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG	
	TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC	
	AAGGGCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGT	
	TCCCTGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTT	
	CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC	
	AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC	
	TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC	
	CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC	
	AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG	
	ACCAACAATGGCTTCATCCCTCACAAC	
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	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG	
	AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA	
	ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA	
	GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG	
	CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG	
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	AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC	
	CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC	
	CTGACACGGGCCATTAACAAGAACAAGTGCGACATCCCTG	
	ACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCG	
	GTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGA	
	ATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTG	
	AGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGG	
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	CGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCA	
	GCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATC	
	GACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTA	
	GCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGG	
	ACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTA	
	CTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCA	
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	CAGAGCAAAGAGTGCAACATCAACATCAGCACCACCAAC	
	TATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT	
	GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA	
	AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT	
	CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC	
	CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC	
	AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG	
	GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC	
	TGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG	
	AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA	
	GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT	
	CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG	
	ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA	
	AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA	
	CAATGGCTTCATCCCTCACAAC	

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
HMPV_ProlineStab_D183P	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC CTGACACGGGCCATTAACAAGAACAAGTGCCCTATCGACG ACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCG GTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGA ATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTG AGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGG CCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGA CGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCA GCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATC GACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTA GCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGG ACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTA CTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCA CGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAG CAGAGCAAAGAGTGCAACATCAACATCAGCACCACCAAC TATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC TGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA CAATGGCTTCATCCCTCACAAC	121
HMPV_ProlineStab_E131P	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG CAGGCGTGGCCATCGCTAAGACCATCAGACTGCCTAGCGA AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA GGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGCC ACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAACC TGACACGGGCCATTAACAAGAACAAGTGCGACATCGACG ACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCG GTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGA ATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTG AGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGG CCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGA CGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCA GCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATC GACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTA GCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGG ACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTA CTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCA CGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAG CAGAGCAAAGAGTGCAACATCAACATCAGCACCACCAAC TATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC TGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG	122

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
	AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA CAATGGCTTCATCCCTCACAAC	
HMPV_ProlineStab_D447P	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC CTGACACGGGCCATTAACAAGAACAAGTGCGACATCGAC GACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGC GGTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGG AATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCT GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG GCCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCG ACGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGC AGCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGA TCGACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTG TAGCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGA GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGAC CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG AGCAGAGCAAAGAGTGCAACATCAACATCAGCACCACCA ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC TATGGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTT ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG GCATCATCAAGCAGCTGAACAAGGGCTGCAGCTACATCAC CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC AAGGGCAGACCTGTGTCCAGCAGCTTCCCACCTATCAAGT TCCCTGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTT CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG ACCAACAATGGCTTCATCCCTCACAAC	123
HMPV_TrimerRepulsionD454N	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC CTGACACGGGCCATTAACAAGAACAAGTGCGACATCGAC GACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGC GGTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGG AATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCT GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG GCCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCG ACGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGC AGCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGA TCGACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTG TAGCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGA GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGAC CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG AGCAGAGCAAAGAGTGCAACATCAACATCAGCACCACCA ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC	124

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
	TATGGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTT	
	ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG	
	GCATCATCAAGCAGCTGAACAAGGGCTGCAGCTACATCAC	
	CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG	
	TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC	
	AAGGGCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGT	
	TCCCTGAGAACCAGTTCCAGGTGGCCCTGGACCAGGTGTT	
	CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC	
	AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC	
	TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC	
	CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC	
	AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG	
	ACCAACAATGGCTTCATCCCTCACAAC	
HMPV_TrimerRepulsionE453N	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	125
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG	
	AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA	
	ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA	
	GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG	
	CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG	
	AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG	
	AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC	
	CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC	
	CTGACACGGGCCATTAACAAGAACAAGTGCGACATCGAC	
	GACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGC	
	GGTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGG	
	AATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCT	
	GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG	
	GCCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCG	
	ACGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGC	
	AGCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGA	
	TCGACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTG	
	TAGCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGA	
	GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG	
	TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGAC	
	CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG	
	AGCAGAGCAAAGAGTGCAACATCAACATCAGCACCACCA	
	ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC	
	TATGGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTT	
	ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG	
	GCATCATCAAGCAGCTGAACAAGGGCTGCAGCTACATCAC	
	CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG	
	TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC	
	AAGGGCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGT	
	TCCCTCAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTT	
	CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC	
	AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC	
	TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC	
	CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC	
	AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG	
	ACCAACAATGGCTTCATCCCTCACAAC	
HMPV_StabilizeAlphaF196W	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	126
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG	
	AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA	
	ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA	
	GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG	
	CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG	
	AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG	
	AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC	
	CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC	
	CTGACACGGGCCATTAACAAGAACAAGTGCGACATCGAC	
	GACCTGAAGATGGCCGTGTCCTTTAGCCAGTGGAACCGGC	
	GGTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGG	
	AATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCT	
	GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG	
	GCCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCG	
	ACGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGC	
	AGCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGA	

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
	TCGACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTG	
	TAGCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGA	
	GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG	
	TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGAC	
	CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG	
	AGCAGAGCAAAGAGTGCAACATCAACATCAGCACCACCA	
	ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC	
	TATGGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTT	
	ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG	
	GCATCATCAAGCAGCTGAACAAGGGCTGCAGCTACATCAC	
	CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG	
	TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC	
	AAGGGCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGT	
	TCCCTGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTT	
	CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC	
	AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC	
	TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC	
	CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC	
	AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG	
	ACCAACAATGGCTTCATCCCTCACAAC	
Human Metapneumovirus mRNA Sequences		
HMPV_SC_DSCAV1_4MMV	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	127
	CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA	
	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCUGCAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCUUUGCCGUGCGCGAGCUGAAGGACUUC	
	GUGUCCAAGAACCUGACACGGGCCCUGAACAAGAACAAG	
	UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC	
	CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU	
	AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC	
	CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC	
	AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG	
	AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU	
	GUGUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC	
	AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA	
	UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC	
	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGGAUCAGUUCAACGUGGCCCUGGACCAGGUGUUCG	
	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU	
	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
	CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG	
	UGACCAACAAUGGCUUCAUCCCUCACAAC	
HMPV_SC_DSURIC_4MMV	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	128
	CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA	
	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCUGCAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG	
	UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC	
	CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU	
	AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC	
	CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC	
	AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG	
	AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU	
	GUGUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC	
	AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA	
	UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC	
	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGCACCAGUGGCAUGUGGCCCUGGACCAGGUGUUCGA	
	GAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCAA	
	CAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCUU	
	CAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCUC	
	CAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGAC	
	CAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAGU	
	GACCAACAAUGGCUUCAUCCCUCACAAC	
HMPV_SC_DM_Krarup_U74LD185P	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	129
	CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA	
	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGCUCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG	
	UGCGACAUCCCUGACCUGAAGAUGGCCGUGUCCUUUAGC	
	CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU	
	AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC	
	CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC	
	AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG	
	AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU	
	GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC	
	AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA	
	UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC	
	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG	
	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU	
	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
	CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG	
	UGACCAACAAUGGCUUCAUCCCUCACAAC	
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TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	CCUGAUCAAGACCGAGCUGGAUCUGCUCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG	
	UGCGACAUCCCUGACCUGAAGAUGGCCGUGUCCUUUAGC	
	CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU	
	AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC	
	CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC	
	AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG	
	AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU	
	GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC	
	AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA	
	UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC	
	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGAACCAGUUCCAGGUGGCCCUGGACCAGGUGUUCGA	
	GAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCAA	
	CAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCUU	
	CAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCUC	
	CAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGAC	
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	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
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	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
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	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
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	CCUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAA	
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	GAAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUC	
	UGAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUG	
	CAGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGG	
	AUUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGG	
	CAAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
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TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
	CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG	
	UGACCAACAAUGGCUUCAUCCCUCACAAC	
HMPV_SC_5M_Krarup_U74LS170LD185PD454N	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	132
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	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGCUCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGCUUAAGAACCUGACACGGGCCAUUAACAAGAACAA	
	GUGCGACAUCCCUGACCUGAAGAUGGCCGUGUCCUUUAG	
	CCAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUU	
	UAGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGA	
	CCUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAA	
	CAUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGA	
	GAAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUC	
	UGAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUG	
	CAGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGG	
	AUUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGG	
	CAAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
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	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
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	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGAACCAGUUCCAGGUGGCCCUGGACCAGGUGUUCGA	
	GAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCAA	
	CAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCUU	
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	CAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGAC	
	CAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAGU	
	GACCAACAAUGGCUUCAUCCCUCACAAC	
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	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGCCUGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
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	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
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	UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC	
	CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU	
	AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC	
	CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC	
	AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG	
	AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU	
	GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC	
	AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA	
	UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC	
	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
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TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG	
	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU	
	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
	CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG	
	UGACCAACAAUGGCUUCAUCCCUCACAAC	
HMPV_SC_UM_Krarup_E51PU74LD454N	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	134
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	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGCCUGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGCUCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG	
	UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC	
	CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU	
	AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC	
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	GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC	
	AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA	
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	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
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	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
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	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGAACCAGUUCCAGGUGGCCCUGGACCAGGUGUUCGA	
	GAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCAA	
	CAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCUU	
	CAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCUC	
	CAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGAC	
	CAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAGU	
	GACCAACAAUGGCUUCAUCCCUCACAAC	
HMPV_SC_SUabilizeAlpha_U74L	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	135
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	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGCUCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
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	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
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	GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG	
	UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC	
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TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA	
	UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC	
	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
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	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG	
	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU	
	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
	CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG	
	UGACCAACAAUGGCUUCAUCCCUCACAAC	
HMPV_SC_SUabilizeAlpha_V55L	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	136
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	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACCUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU	
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	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
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	CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU	
	AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC	
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	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG	
	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU	
	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
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	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
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TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	GUGCUUAAGAACCUGACACGGGCCAUUAACAAGAACAA	
	GUGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAG	
	CCAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUU	
	UAGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGA	
	CCUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAA	
	CAUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGA	
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	UGAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUG	
	CAGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGG	
	AUUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGG	
	CAAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
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	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG	
	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU	
	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
	CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG	
	UGACCAACAAUGGCUUCAUCCCUCACAAC	
HMPV_SC_SUabilizeAlpha_U174W	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	138
	CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA	
	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGUCCAAGAACCUGUGGCGGGCCAUUAACAAGAACAA	
	GUGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAG	
	CCAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUU	
	UAGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGA	
	CCUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAA	
	CAUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGA	
	GAAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUC	
	UGAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUG	
	CAGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGG	
	AUUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGG	
	CAAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG	
	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU	
	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
	CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG	
	UGACCAACAAUGGCUUCAUCCCUCACAAC	

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
HMPV_SC_4M_SUabilize-Alpha_V55LU74LS170LU174W	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU GGGCGACCUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG CCUGAUCAAGACCGAGCUGGAUCUGCUCAAGAGCGCCCU GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC GUGCUUAAGAACCUGUGGCGGGCCAUUAACAAGAACAA GUGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAG CCAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUU UAGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGA CCUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAA CAUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGA GAAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUC UGAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUG CAGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGG AUUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGG CAAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG UGACCAACAAUGGCUUCAUCCCUCACAAC	139
HMPV_ProlineSUab_E51P	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU GAGAACCGGCUGGUACACCAACGUGUUCACACUGCCUGU GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	140

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG	
	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU	
	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
	CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG	
	UGACCAACAAUGGCUUCAUCCCUCACAAC	
HMPV_ProlineSUab_D185P	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	141
	CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA	
	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG	
	UGCGACAUCCCUGACCUGAAGAUGGCCGUGUCCUUUAGC	
	CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU	
	AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC	
	CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC	
	AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG	
	AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU	
	GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC	
	AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA	
	UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC	
	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG	
	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU	
	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
	CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG	
	UGACCAACAAUGGCUUCAUCCCUCACAAC	
HMPV_ProlineSUab_D183P	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	142
	CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA	
	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
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	GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG	
	UGCCCUAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC	
	CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU	
	AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC	
	CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC	
	AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG	
	AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU	
	GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC	
	AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA	
	UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC	
	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
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	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG	
	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU	
	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
	CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG	
	UGACCAACAAUGGCUUCAUCCCUCACAAC	
HMPV_ProlineSUab_E131P	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	143
	CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA	
	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGCCUAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG	
	UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC	
	CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU	
	AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC	
	CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC	
	AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG	
	AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU	
	GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC	
	AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA	
	UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC	
	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
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	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
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	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG	
	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU	
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	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
	CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG	
	UGACCAACAAUGGCUUCAUCCCUCACAAC	
HMPV_ProlineSUab_D447P	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	144
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	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG	
	UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC	
	CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU	

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
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	AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU	
	GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC	
	AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA	
	UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC	
	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCCCACCUAUCAAGUUCCC	
	UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG	
	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU	
	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
	CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG	
	UGACCAACAAUGGCUUCAUCCCUCACAAC	
HMPV_UrimerRepulsionD454N	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	145
	CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA	
	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG	
	UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC	
	CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU	
	AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC	
	CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC	
	AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG	
	AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU	
	GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC	
	AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA	
	UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC	
	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGAACCAGUUCCAGGUGGCCCUGGACCAGGUGUUCGA	
	GAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCAA	
	CAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCUU	
	CAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCUC	
	CAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGAC	
	CAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAGU	
	GACCAACAAUGGCUUCAUCCCUCACAAC	
HMPV_UrimerRepulsionE453N	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	146
	CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA	
	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG	
	UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC	
	CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU	
	AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC	
	CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC	
	AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG	
	AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU	
	GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC	
	AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA	
	UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC	
	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UCAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCGA	
	GAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCAA	
	CAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCUU	
	CAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCUC	
	CAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGAC	
	CAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAGU	
	GACCAACAAUGGCUUCAUCCCUCACAAC	
HMPV_SUabilizeAlphaF196W	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	147
	CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA	
	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG	
	UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC	
	CAGUGGAACCGGCGGUUUCUGAACGUCGUGCGGCAGUU	
	UAGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGA	
	CCUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAA	
	CAUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGA	
	GAAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUC	
	UGAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUG	
	CAGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGG	
	AUUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGG	
	CAAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG	
	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU	

TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG UGACCAACAAUGGCUUCAUCCCUCACAAC	

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the disclosure described herein. Such equivalents are intended to be encompassed by the following claims.

All references, including patent documents, disclosed herein are incorporated by reference in their entirety.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 147

<210> SEQ ID NO 1
<211> LENGTH: 1620
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Human metapneumovirus

<400> SEQUENCE: 1

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gagagctacc tggaagagag ctgctccacc atcaccgagg gctacctgag cgtgctgcgg 120

accggctggt acaccaacgt gttcaccctg gaggtgggcg acgtggagaa cctgacctgc 180

agcgacggcc ctagcctgat caagaccgag ctggacctga ccaagagcgc tctgagagag 240

ctgaagaccg tgtccgccga ccagctggcc agagaggaac agatcgagaa ccctcggcag 300

agcagattcg tgctgggcgc catcgctctg ggagtcgccg ctgccgctgc agtgacagct 360

ggagtggcca ttgctaagac catcagactg gaaagcgagg tgacagccat caacaatgcc 420

ctgaagaaga ccaacgaggc cgtgagcacc ctgggcaatg gagtgagagt gctggccaca 480

gccgtgcggg agctgaagga cttcgtgagc aagaacctga ccagagccat caacaagaac 540

aagtgcgaca tcgatgacct gaagatggcc gtgagcttct cccagttcaa cagacggttc 600

ctgaacgtgg tgagacagtt ctccgacaac gctggaatca cacctgccat tagcctggac 660

ctgatgaccg acgccgagct ggctagagcc gtgcccaaca tgcccaccag cgctggccag 720

atcaagctga tgctggagaa cagagccatg gtgcggagaa agggcttcgg catcctgatt 780

ggggtgtatg gaagctccgt gatctacatg gtgcagctgc ccatcttcgg cgtgatcgac 840

acaccctgct ggatcgtgaa ggccgctcct agctgctccg agaagaaagg aaactatgcc 900

tgtctgctga gagaggacca gggctggtac tgccagaacg ccggaagcac agtgtactat 960

cccaacgaga aggactgcga gaccagaggc gaccacgtgt tctgcgacac cgctgccgga 1020

atcaacgtgg ccgagcagag caaggagtgc aacatcaaca tcagcacaac caactacccc 1080

tgcaaggtga gcaccggacg gcaccccatc agcatggtgg ctctgagccc tctgggcgct 1140

ctggtggcct gctataaggg cgtgtcctgt agcatcggca gcaatcgggt gggcatcatc 1200

aagcagctga acaagggatg ctcctacatc accaaccagg acgccgacac cgtgaccatc 1260

gacaacaccg tgtaccagct gagcaaggtg gagggcgagc agcacgtgat caagggcaga 1320

cccgtgagct ccagcttcga ccccatcaag ttccctgagg accagttcaa cgtggccctg 1380

gaccaggtgt ttgagaacat cgagaacagc caggccctgg tggaccagag caacagaatc 1440

ctgtccagcg ctgagaaggg caacaccggc ttcatcattg tgatcattct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgagcatc ttcatcatta tcaagaagac caagaaaccc 1560

accggagccc ctcctgagct gagcggcgtg accaacaatg gcttcattcc ccacaactga 1620

<210> SEQ ID NO 2
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<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Human metapneumovirus

<400> SEQUENCE: 2

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gagagttatt tggaagaatc atgtagtact ataactgagg gatacctcag tgttttaaga 120

acaggctggt acactaatgt cttcacatta gaagttggtg atgttgaaaa tcttacatgt 180

actgatggac ctagcttaat caaaacagaa cttgatctaa caaaaagtgc tttaagggaa 240

ctcaaaacag tctctgctga tcagttggcg agagaggagc aaattgaaaa tcccagacaa 300

tcaagatttg tcttaggtgc gatagctctc ggagttgcta cagcagcagc agtcacagca 360

ggcattgcaa tagccaaaac cataaggctt gagagtgagg tgaatgcaat taaaggtgct 420

ctcaaacaaa ctaatgaagc agtatccaca ttagggaatg gtgtgcgggt cctagccact 480

gcagtgagag agctaaaaga atttgtgagc aaaaacctga ctagtgcaat caacaggaac 540

aaatgtgaca ttgctgatct gaagatggct gtcagcttca gtcaattcaa cagaagattt 600

ctaaatgttg tgcggcagtt ttcagacaat gcagggataa caccagcaat atcattggac 660

ctgatgactg atgctgagtt ggccagagct gtatcataca tgccaacatc tgcagggcag 720

ataaaactga tgttggagaa ccgcgcaatg gtaaggagaa aaggatttgg aatcctgata 780

ggggtctacg gaagctctgt gatttacatg gttcaattgc cgatctttgg tgtcatagat 840

acaccttgtt ggatcatcaa ggcagctccc tcttgctcag aaaaaaacgg gaattatgct 900

tgcctcctaa gagaggatca agggtggtat tgtaaaaatg caggatctac tgtttactac 960

ccaaatgaaa aagactgcga aacaagaggt gatcatgttt tttgtgacac agcagcaggg 1020

atcaatgttg ctgagcaatc aagagaatgc aacatcaaca tatctactac caactaccca 1080

tgcaaagtca gcacaggaag acaccctata agcatggttg cactatcacc tctcggtgct 1140

ttggtggctt gctataaagg ggtaagctgc tcgattggca gcaattgggt tggaatcatc 1200

aaacaattac ccaaaggctg ctcatacata accaaccagg atgcagacac tgtaacaatt 1260

gacaataccg tgtatcaact aagcaaagtt gaaggtgaac agcatgtaat aaaagggaga 1320

ccagtttcaa gcagttttga tccaatcaag tttcctgagg atcagttcaa tgttgcgctt 1380

gatcaagtct tcgaaagcat tgagaacagt caggcactag tggaccagtc aaacaaaatt 1440

ctaaacagtg cagaaaaagg aaacactggt ttcattatcg tagtaatttt ggttgctgtt 1500

cttggtctaa ccatgatttc agtgagcatc atcatcataa tcaagaaaac aaggaagccc 1560

acaggagcac ctccagagct gaatggtgtc accaacggcg gtttcatacc acatagttag 1620

<210> SEQ ID NO 3
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<212> TYPE: DNA
<213> ORGANISM: Unknown

<220> FEATURE:
<223> OTHER INFORMATION: Human metapneumovirus

<400> SEQUENCE: 3

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acaggttggt acaccaatgt ctttacatta gaagttggtg atgttgaaaa tcttacatgt 180

actgatggac ctagcttaat caaaacagaa cttgacctaa ccaaaagtgc tttaagagaa 240

ctcaaaacag tttctgctga tcagttagcg agagaagaac aaattgaaaa tcccagacaa 300

tcaaggtttg tcctaggtgc aatagctctt ggagttgcca cagcagcagc agtcacagca 360

ggcattgcaa tagccaaaac tataaggctt gagagtgaag tgaatgcaat caaaggtgct 420

ctcaaaacaa ccaatgaggc agtatcaaca ctaggaaatg gagtgcgggt cctagccact 480

gcagtaagag agctgaaaga atttgtgagc aaaaacctga ctagtgcgat caacaagaac 540

aagtgtgaca ttgctgattt gaagatggct gtcagcttca gtcagttcaa cagaagattc 600

ctaaatgttg tgcggcagtt ttcagacaat gcagggataa caccagcaat atcattggac 660

ctgatgaatg atgctgagct ggccagagct gtatcataca tgccaacatc tgcaggacag 720

ataaaactaa tgttagagaa ccgtgcaatg gtgaggagaa aaggatttgg aatcttgata 780

ggggtctacg gaagctctgt gatttacatg gtccagctgc cgatctttgg tgtcataaat 840

acaccttgtt ggataatcaa ggcagctccc tcttgttcag aaaaagatgg aaattatgct 900

tgcctcctaa gagaggatca agggtggtat tgtaaaaatg caggatccac tgtttactac 960

ccaaatgaaa aagactgcga aacaagaggt gatcatgttt tttgtgacac agcagcaggg 1020

atcaatgttg ctgagcaatc aagagaatgc aacatcaaca tatctaccac caactaccca 1080

tgcaaagtca gcacaggaag acaccctatc agcatggttg cactatcacc tctcggtgct 1140

ttggtagctt gctacaaagg ggttagctgc tcgactggca gtaatcaggt tggaataatc 1200

aaacaactac ctaaaggctg ctcatacata actaaccagg acgcagacac tgtaacaatt 1260

gacaacactg tgtatcaact aagcaaagtt gagggtgaac agcatgtaat aaaagggaga 1320

ccagtttcaa gcagttttga tccaatcagg tttcctgagg atcagttcaa tgttgcgctt 1380

gatcaagtct ttgaaagcat tgaaaacagt caagcactag tggaccagtc aaacaaaatt 1440

ctgaacagtg cagaaaaagg aaacactggt ttcattattg taataatttt gattgctgtt 1500

cttgggttaa ccatgatttc agtgagcatc atcatcataa tcaaaaaaac aaggaagccc 1560

acaggggcac ctccggagct gaatggtgtt accaacggcg gtttcatacc gcatagttag 1620

<210> SEQ ID NO 4
<211> LENGTH: 1725
<212> TYPE: DNA
<213> ORGANISM: Human respiratory syncytial virus

<400> SEQUENCE: 4

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tgtttcgctt ccagtcaaaa catcactgaa gaatttttatc aatcaacatg cagtgcagtt 120

agcaaaggct atcttagtgc tctaagaact ggttggtata ctagtgttat aactatagaa 180

ttaagtaata tcaaggaaaa taagtgtaat ggaacagatg ctaaggtaaa attgataaaa 240

caagaattag ataaatataa aaatgctgta acagaattgc agttgctcat gcaaagcaca 300

ccagcagcca acaatcgagc cagaagagaa ctaccaaggt ttatgaatta tacactcaat 360

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aataccaaaa ataccaatgt aacattaagc aagaaaagga aaagaagatt tcttggcttt    420

ttgttaggtg ttggatctgc aatcgccagt ggcattgctg tatctaaggt cctgcaccta    480

gaaggggaag tgaacaaaat caaaagtgct ctactatcca caaacaaggc tgtagtcagc    540

ttatcaaatg gagttagtgt cttaaccagc aaagtgttag acctcaaaaa ctatatagat    600

aaacagttgt tacctattgt gaacaagcaa agctgcagca tatcaaacat tgaaactgtg    660

atagagttcc aacaaaagaa caacagacta ctagagatta ccagggaatt tagtgttaat    720

gcaggtgtaa ctacacctgt aagcacttat atgttaacta atagtgaatt attatcatta    780

atcaatgata tgcctataac aaatgatcag aaaaagttaa tgtccaacaa tgttcaaata    840

gttagacagc aaagttactc tatcatgtcc ataataaagg aggaagtctt agcatatgta    900

gtacaattac cactatatgg tgtaatagat acaccctgtt ggaaactgca cacatcccct    960

ctatgtacaa ccaacacaaa ggaagggtcc aacatctgct taacaagaac cgacagagga   1020

tggtattgtg acaatgcagg atcagtatct ttcttcccac aagctgaaac atgtaaagtt   1080

caatcgaatc gggtattttg tgacacaatg aacagtttaa cattaccaag tgaagtaaat   1140

ctctgcaaca ttgacatatt caaccccaaa tatgattgca aaattatgac ttcaaaaaca   1200

gatgtaagca gctccgttat cacatctcta ggagccattg tgtcatgcta tggcaaaact   1260

aaatgtacag catccaataa aaatcgtggg atcataaaga cattttctaa cgggtgtgat   1320

tatgtatcaa ataaggggtt ggatactgtg tctgtaggta atacattata ttatgtaaat   1380

aagcaagaag gcaaaagtct ctatgtaaaa ggtgaaccaa taataaattt ctatgaccca   1440

ttagtgttcc cctctgatga atttgatgca tcaatatctc aagtcaatga gaagattaac   1500

cagagcctag catttattcg taaatccgat gaattattac ataatgtaaa tgctggtaaa   1560

tccaccacaa atatcatgat aactactata attatagtga ttatagtaat attgttatca   1620

ttaattgcag ttggactgct cctatactgc aaggccagaa gcacaccagt cacactaagt   1680

aaggatcaac tgagtggtat aaataatatt gcatttagta actga                   1725
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<210> SEQ ID NO 5
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Human metapneumovirus isolate

<400> SEQUENCE: 5

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Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                  10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Arg Gln Ser Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125
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Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535
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<210> SEQ ID NO 6
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Human metapneumovirus

<400> SEQUENCE: 6

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His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Arg Gln Ser Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Thr Ala Ala Ala Val Thr Ala Gly Ile Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Asn Ala Ile Lys Gly Ala Leu Lys Gln Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Glu Phe Val Ser Lys Asn Leu Thr Ser Ala
                165                 170                 175

Ile Asn Arg Asn Lys Cys Asp Ile Ala Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Ser Tyr Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Asn Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365
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Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Trp Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Ser Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Lys Ile
465                 470                 475                 480

Leu Asn Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Val Ile
                485                 490                 495

Leu Val Ala Val Leu Gly Leu Thr Met Ile Ser Val Ser Ile Ile Ile
            500                 505                 510

Ile Ile Lys Lys Thr Arg Lys Pro Thr Gly Ala Pro Pro Glu Leu Asn
        515                 520                 525

Gly Val Thr Asn Gly Gly Phe Ile Pro His Ser
    530                 535


<210> SEQ ID NO 7
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Human metapneumovirus

<400> SEQUENCE: 7

Met Ser Trp Lys Val Met Ile Ile Ile Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Arg Gln Ser Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Thr Ala Ala Ala Val Thr Ala Gly Ile Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Asn Ala Ile Lys Gly Ala Leu Lys Thr Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Glu Phe Val Ser Lys Asn Leu Thr Ser Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Ala Asp Leu Lys Met Ala Val Ser
            180                 185                 190
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Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Asn Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Ser Tyr Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asn Thr Pro Cys Trp Ile Ile Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Thr Gly Ser Asn Gln Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Arg Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Ser Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Lys Ile
465                 470                 475                 480

Leu Asn Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Leu Thr Met Ile Ser Val Ser Ile Ile Ile
            500                 505                 510

Ile Ile Lys Lys Thr Arg Lys Pro Thr Gly Ala Pro Pro Glu Leu Asn
        515                 520                 525

Gly Val Thr Asn Gly Gly Phe Ile Pro His Ser
    530                 535


<210> SEQ ID NO 8
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Human respiratory syncytial virus

<400> SEQUENCE: 8

Met Glu Leu Pro Ile Leu Lys Thr Asn Ala Ile Thr Thr Ile Leu Ala
1               5                   10                  15

Ala Val Thr Leu Cys Phe Ala Ser Ser Gln Asn Ile Thr Glu Glu Phe
            20                  25                  30
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Tyr Gln Ser Thr Cys Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu
        35                  40                  45

Arg Thr Gly Trp Tyr Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile
    50                  55                  60

Lys Glu Asn Lys Cys Asn Gly Thr Asp Ala Lys Val Lys Leu Ile Lys
65                  70                  75                  80

Gln Glu Leu Asp Lys Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu
                85                  90                  95

Met Gln Ser Thr Pro Ala Ala Asn Asn Arg Ala Arg Arg Glu Leu Pro
            100                 105                 110

Arg Phe Met Asn Tyr Thr Leu Asn Asn Thr Lys Asn Thr Asn Val Thr
        115                 120                 125

Leu Ser Lys Lys Arg Lys Arg Arg Phe Leu Gly Phe Leu Leu Gly Val
    130                 135                 140

Gly Ser Ala Ile Ala Ser Gly Ile Ala Val Ser Lys Val Leu His Leu
145                 150                 155                 160

Glu Gly Glu Val Asn Lys Ile Lys Ser Ala Leu Leu Ser Thr Asn Lys
                165                 170                 175

Ala Val Val Ser Leu Ser Asn Gly Val Ser Val Leu Thr Ser Lys Val
            180                 185                 190

Leu Asp Leu Lys Asn Tyr Ile Asp Lys Gln Leu Leu Pro Ile Val Asn
        195                 200                 205

Lys Gln Ser Cys Ser Ile Ser Asn Ile Glu Thr Val Ile Glu Phe Gln
    210                 215                 220

Gln Lys Asn Asn Arg Leu Leu Glu Ile Thr Arg Glu Phe Ser Val Asn
225                 230                 235                 240

Ala Gly Val Thr Thr Pro Val Ser Thr Tyr Met Leu Thr Asn Ser Glu
                245                 250                 255

Leu Leu Ser Leu Ile Asn Asp Met Pro Ile Thr Asn Asp Gln Lys Lys
            260                 265                 270

Leu Met Ser Asn Asn Val Gln Ile Val Arg Gln Gln Ser Tyr Ser Ile
        275                 280                 285

Met Ser Ile Ile Lys Glu Glu Val Leu Ala Tyr Val Val Gln Leu Pro
    290                 295                 300

Leu Tyr Gly Val Ile Asp Thr Pro Cys Trp Lys Leu His Thr Ser Pro
305                 310                 315                 320

Leu Cys Thr Thr Asn Thr Lys Glu Gly Ser Asn Ile Cys Leu Thr Arg
                325                 330                 335

Thr Asp Arg Gly Trp Tyr Cys Asp Asn Ala Gly Ser Val Ser Phe Phe
            340                 345                 350

Pro Gln Ala Glu Thr Cys Lys Val Gln Ser Asn Arg Val Phe Cys Asp
        355                 360                 365

Thr Met Asn Ser Leu Thr Leu Pro Ser Glu Val Asn Leu Cys Asn Ile
    370                 375                 380

Asp Ile Phe Asn Pro Lys Tyr Asp Cys Lys Ile Met Thr Ser Lys Thr
385                 390                 395                 400

Asp Val Ser Ser Ser Val Ile Thr Ser Leu Gly Ala Ile Val Ser Cys
                405                 410                 415

Tyr Gly Lys Thr Lys Cys Thr Ala Ser Asn Lys Asn Arg Gly Ile Ile
            420                 425                 430

Lys Thr Phe Ser Asn Gly Cys Asp Tyr Val Ser Asn Lys Gly Val Asp
        435                 440                 445
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Thr Val Ser Val Gly Asn Thr Leu Tyr Tyr Val Asn Lys Gln Glu Gly
    450                 455                 460

Lys Ser Leu Tyr Val Lys Gly Glu Pro Ile Ile Asn Phe Tyr Asp Pro
465                 470                 475                 480

Leu Val Phe Pro Ser Asp Glu Phe Asp Ala Ser Ile Ser Gln Val Asn
                485                 490                 495

Glu Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg Lys Ser Asp Glu Leu
            500                 505                 510

Leu His Asn Val Asn Ala Gly Lys Ser Thr Thr Asn Ile Met Ile Thr
        515                 520                 525

Thr Ile Ile Ile Val Ile Ile Val Ile Leu Leu Ser Leu Ile Ala Val
    530                 535                 540

Gly Leu Leu Leu Tyr Cys Lys Ala Arg Ser Thr Pro Val Thr Leu Ser
545                 550                 555                 560

Lys Asp Gln Leu Ser Gly Ile Asn Asn Ile Ala Phe Ser Asn
                565                 570


<210> SEQ ID NO 9
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Human parainfluenza virus 3

<400> SEQUENCE: 9

atgccaattt caatactgtt aattattaca accatgatca tggcatcaca ctgccaaata     60

gacatcacaa aactacagca tgtaggtgta ttggtcaaca gtcccaaagg gatgaagata    120

tcacaaaact tcgaaacaag atatctaatc ctgagtctca taccaaaaat agaagattct    180

aactcttgtg gtgaccaaca gatcaagcaa tacaagaggt tattggatag actgatcatt    240

cctttatatg atggactaag attacagaag gatgtgatag tgactaatca agaatccaat    300

gaaaacactg atcccagaac agaacgattc tttggagggg taattggaac tattgctcta    360

ggagtagcaa cctcagcaca aattacagca gcagttgctc tggttgaagc caagcaggca    420

agatcagaca ttgaaaaact caaggaagca atcagggaca caaataaagc agtgcagtca    480

gttcagagct ctgtaggaaa tttgatagta gcaattaaat cagtccagga ttatgtcaac    540

aaagaaatcg tgccatcgat tgcgagacta ggttgtgaag cagcaggact tcagttaggg    600

attgcattaa cacagcatta ctcagaatta acaaatatat ttggtgataa cataggatcg    660

ttacaagaaa aaggaataaa attacaaggt atagcatcat tataccgtac aaatatcaca    720

gaaatattca caacatcaac agttgacaaa tatgatattt atgatctatt atttacagaa    780

tcaataaagg tgagagttat agatgttgat ttgaatgatt actcaataac cctccaagtc    840

agactccctt tattgaccag actgctgaac actcaaatct acaaagtaga ttccatatca    900

tacaatatcc aaaatagaga atggtatatc cctcttccca gccatatcat gacgaaaggg    960

gcatttctag gtggagcaga tgtcaaagaa tgcatagaag cattcagcag ttatatatgc   1020

ccttctgatc caggatttgt actaaaccat gaaatggaga gctgtctatc aggaaacata   1080

tcccaatgtc caagaaccac agtcacatca gacatagttc ctaggtatgc atttgtcaat   1140

ggaggagtgg ttgcgaattg tataacaact acatgtacat gcaatggtat cggtaataga   1200

atcaaccaac cacctgatca aggagtcaaa attataacac ataaagaatg taatacaata   1260

ggtatcaacg gaatgctatt caacacaaac aaagaaggaa ctcttgcatt ctacacacca   1320

gacgacataa cattaaacaa ttctgttgca cttgatccga ttgacatatc aatcgagctc   1380

aacaaggcca aatcagatct tgaggaatca aaagaatgga taagaaggtc aaatcaaaag   1440
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ctagattcta ttggaagttg gcatcaatct agcactacaa tcatagttat tttgataatg 1500

atgattatat tgtttataat taatataaca ataattacaa ttgcaattaa gtattacaga 1560

attcaaaaga gaaatcgagt ggatcaaaat gataagccgt atgtattaac aaacaag 1617

<210> SEQ ID NO 10
<211> LENGTH: 1716
<212> TYPE: DNA
<213> ORGANISM: Human parainfluenza virus 3

<400> SEQUENCE: 10

atggaatact ggaagcacac caaccacgga aaggatgctg gtaatgagct ggagacatcc 60

acagccactc atggcaacaa gctcaccaac aagataacat atatattgtg gacgataacc 120

ctggtgttat tatcaatagt cttcatcata gtgctaacta attccatcaa aagtgaaaag 180

gcccgcgaat cattgctaca agacataaat aatgagttta tggaagttac agaaaagatc 240

caagtggcat cggataatac taatgatcta atacagtcag gagtgaatac aaggcttctt 300

acaattcaga gtcatgtcca gaattatata ccaatatcat tgacacaaca aatatcggat 360

cttaggaaat tcattagtga aattacaatt agaaatgata atcaagaagt gccaccacaa 420

agaataacac atgatgtggg tataaaacct ttaaatccag atgatttctg gagatgcacg 480

tctggtcttc catctttgat gaaaactcca aaaataagat taatgccggg accaggatta 540

ttagctatgc caacgactgt tgatggctgt gtcagaaccc cgtccttagt gataaatgat 600

ctgatttatg cttacacctc aaatctaatt actcgaggtt gccaggatat agggaaatca 660

tatcaagtat tacagatagg gataataact gtaaactcag acttggtacc tgacttaaat 720

cctaggatct ctcatacctt caacataaat gacaatagaa agtcatgttc tctagcactc 780

ctaaatacag atgtatatca actgtgttca accccaaaag ttgatgaaag atcagattat 840

gcatcatcag gcatagaaga tattgtactt gatattgtca attatgatgg ctcaatctcg 900

acaacaagat ttaagaataa taatataagt tttgatcaac catatgcggc attataccca 960

tctgttggac cagggatata ctacaaaggc aaaataatat ttctcgggta tggaggtctt 1020

gaacatccaa taaatgagaa tgcaatctgc aacacaactg ggtgtcctgg gaaaacacag 1080

agagactgta atcaagcatc tcatagtcca tggttttcag atagaaggat ggtcaactct 1140

ataattgttg ttgacaaggg cttgaactca gttccaaaat tgaaggtatg gacgatatct 1200

atgagacaaa attactgggg gtcagaagga agattacttc tactaggtaa caagatctac 1260

atatacacaa gatctacaag ttggcacagc aagttacaat taggaataat tgacattact 1320

gactacagtg atataaggat aaaatggaca tggcataatg tgctatcaag accaggaaac 1380

aatgaatgtc catggggaca ttcatgtccg gatggatgta taacgggagt atataccgat 1440

gcatatccac tcaatcccac aggaagcatt gtatcatctg tcatattgga ctcacaaaaa 1500

tcgagagtca acccagtcat aacttactca acagcaaccg aaagggtaaa cgagctggct 1560

atccgaaaca aaacactctc agctgggtac acaacaacaa gctgcattac acactataac 1620

aaagggtatt gttttcatat agtagaaata aatcataaaa gcttaaacac atttcaaccc 1680

atgttgttca aaacagagat tccaaaaagc tgcagt 1716

<210> SEQ ID NO 11
<211> LENGTH: 1716
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 11

atggaatact ggaagcacac caaccacggc aaggacgccg gcaacgagct ggaaaccagc 60

acagccacac acggcaacaa gctgaccaac aagatcacct acatcctgtg gaccatcacc 120

ctggtgctgc tgagcatcgt gttcatcatc gtgctgacca atagcatcaa gagcgagaag 180

gccagagaga gcctgctgca ggacatcaac aacgagttca tggaagtgac cgagaagatc 240

caggtggcca gcgacaacac caacgacctg atccagagcg gcgtgaacac ccggctgctg 300

accatccaga gccacgtgca gaactacatc cccatcagcc tgacccagca gatcagcgac 360

ctgcggaagt tcatcagcga gatcaccatc cggaacgaca accaggaagt gccccccag 420

agaatcaccc acgacgtggg catcaagccc ctgaaccccg acgatttctg gcggtgtaca 480

agcggcctgc ccagcctgat gaagaccccc aagatccggc tgatgcctgg ccctggactg 540

ctggccatgc ctaccacagt ggatggctgt gtgcggaccc ccagcctcgt gatcaacgat 600

ctgatctacg cctacaccag caacctgatc acccggggct gccaggatat cggcaagagc 660

taccaggtgc tgcagatcgg catcatcacc gtgaactccg acctggtgcc cgacctgaac 720

cctcggatca gccacacctt caacatcaac gacaacagaa agagctgcag cctggctctg 780

ctgaacaccg acgtgtacca gctgtgcagc acccccaagg tggacgagag aagcgactac 840

gccagcagcg gcatcgagga tatcgtgctg gacatcgtga actacgacgg cagcatcagc 900

accacccggt tcaagaacaa caacatcagc ttcgaccagc cctacgccgc cctgtaccct 960

tctgtgggcc ctggcatcta ctacaagggc aagatcatct tcctgggcta cggcggcctg 1020

gaacacccca tcaacgagaa cgccatctgc aacaccaccg gctgccctgg caagacccag 1080

agagactgca atcaggccag ccacagcccc tggttcagcg accgcagaat ggtcaactct 1140

atcatcgtgg tggacaaggg cctgaacagc gtgcccaagc tgaaagtgtg gacaatcagc 1200

atgcgccaga actactgggg cagcgagggc agacttctgc tgctgggaaa caagatctac 1260

atctacaccc ggtccaccag ctggcacagc aaactgcagc tgggaatcat cgacatcacc 1320

gactacagcg acatccggat caagtggacc tggcacaacg tgctgagcag acccggcaac 1380

aatgagtgcc cttggggcca cagctgcccc gatggatgta tcaccggcgt gtacaccgac 1440

gcctaccccc tgaatcctac cggctccatc gtgtccagcg tgatcctgga cagccagaaa 1500

agcagagtga accccgtgat cacatacagc accgccaccg agagagtgaa cgaactggcc 1560

atcagaaaca agaccctgag cgccggctac accaccacaa gctgcatcac acactacaac 1620

aagggctact gcttccacat cgtggaaatc aaccacaagt ccctgaacac cttccagccc 1680

atgctgttca agaccgagat ccccaagagc tgctcc 1716

<210> SEQ ID NO 12
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 12

atgcccatca gcatcctgct gatcatcacc acaatgatca tggccagcca ctgccagatc 60

gacatcacca agctgcagca cgtgggcgtg ctcgtgaaca gccccaaggg catgaagatc 120

agccagaact tcgagacacg ctacctgatc ctgagcctga tccccaagat cgaggacagc 180

aacagctgcg gcgaccagca gatcaagcag tacaagcggc tgctggacag actgatcatc 240

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cccctgtacg acggcctgcg gctgcagaaa gacgtgatcg tgaccaacca ggaaagcaac    300

gagaacaccg acccccggac cgagagattc ttcggcggcg tgatcggcac aatcgccctg    360

ggagtggcca caagcgccca gattacagcc gctgtggccc tggtggaagc caagcaggcc    420

agaagcgaca tcgagaagct gaaagaggcc atccgggaca ccaacaaggc cgtgcagagc    480

gtgcagtcca gcgtgggcaa tctgatcgtg gccatcaagt ccgtgcagga ctacgtgaac    540

aaagaaatcg tgccctctat cgcccggctg ggctgtgaag ctgccggact gcagctgggc    600

attgccctga cacagcacta cagcgagctg accaacatct tcggcgacaa catcggcagc    660

ctgcaggaaa agggcattaa gctgcaggga atcgccagcc tgtaccgcac caacatcacc    720

gagatcttca ccaccagcac cgtggataag tacgacatct acgacctgct gttcaccgag    780

agcatcaaag tgcgcgtgat cgacgtggac ctgaacgact acagcatcac cctgcaagtg    840

cggctgcccc tgctgaccag actgctgaac acccagatct acaaggtgga cagcatctcc    900

tacaacatcc agaaccgcga gtggtacatc cctctgccca gccacattat gaccaagggc    960

gcctttctgg gcggagccga cgtgaaagag tgcatcgagg ccttcagcag ctacatctgc   1020

cccagcgacc ctggcttcgt gctgaaccac gagatggaaa gctgcctgag cggcaacatc   1080

agccagtgcc ccagaaccac cgtgacctcc gacatcgtgc ccagatacgc cttcgtgaat   1140

ggcggcgtgg tggccaactg catcaccacc acctgtacct gcaacggcat cggcaaccgg   1200

atcaaccagc ctcccgatca gggcgtgaag attatcaccc acaaagagtg taacaccatc   1260

ggcatcaacg gcatgctgtt caataccaac aaagagggca ccctggcctt ctacaccccc   1320

gacgatatca ccctgaacaa ctccgtggct ctggacccca tcgacatctc catcgagctg   1380

aacaaggcca agagcgacct ggaagagtcc aaagagtgga tccggcggag caaccagaag   1440

ctggactcta tcggcagctg gcaccagagc agcaccacca tcatcgtgat cctgattatg   1500

atgattatcc tgttcatcat caacattacc atcatcacta tcgccattaa gtactaccgg   1560

atccagaaac ggaaccgggt ggaccagaat gacaagccct acgtgctgac aaacaag      1617


<210> SEQ ID NO 13
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Human parainfluenza virus 3

<400> SEQUENCE: 13

Met Pro Ile Ser Ile Leu Leu Ile Ile Thr Thr Met Ile Met Ala Ser
1               5                   10                  15

His Cys Gln Ile Asp Ile Thr Lys Leu Gln His Val Gly Val Leu Val
            20                  25                  30

Asn Ser Pro Lys Gly Met Lys Ile Ser Gln Asn Phe Glu Thr Arg Tyr
        35                  40                  45

Leu Ile Leu Ser Leu Ile Pro Lys Ile Glu Asp Ser Asn Ser Cys Gly
    50                  55                  60

Asp Gln Gln Ile Lys Gln Tyr Lys Arg Leu Leu Asp Arg Leu Ile Ile
65                  70                  75                  80

Pro Leu Tyr Asp Gly Leu Arg Leu Gln Lys Asp Val Ile Val Thr Asn
                85                  90                  95

Gln Glu Ser Asn Glu Asn Thr Asp Pro Arg Thr Glu Arg Phe Phe Gly
            100                 105                 110

Gly Val Ile Gly Thr Ile Ala Leu Gly Val Ala Thr Ser Ala Gln Ile
        115                 120                 125
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Thr Ala Ala Val Ala Leu Val Glu Ala Lys Gln Ala Arg Ser Asp Ile
    130                 135                 140

Glu Lys Leu Lys Glu Ala Ile Arg Asp Thr Asn Lys Ala Val Gln Ser
145                 150                 155                 160

Val Gln Ser Ser Val Gly Asn Leu Ile Val Ala Ile Lys Ser Val Gln
                165                 170                 175

Asp Tyr Val Asn Lys Glu Ile Val Pro Ser Ile Ala Arg Leu Gly Cys
            180                 185                 190

Glu Ala Ala Gly Leu Gln Leu Gly Ile Ala Leu Thr Gln His Tyr Ser
        195                 200                 205

Glu Leu Thr Asn Ile Phe Gly Asp Asn Ile Gly Ser Leu Gln Glu Lys
    210                 215                 220

Gly Ile Lys Leu Gln Gly Ile Ala Ser Leu Tyr Arg Thr Asn Ile Thr
225                 230                 235                 240

Glu Ile Phe Thr Thr Ser Thr Val Asp Lys Tyr Asp Ile Tyr Asp Leu
                245                 250                 255

Leu Phe Thr Glu Ser Ile Lys Val Arg Val Ile Asp Val Asp Leu Asn
            260                 265                 270

Asp Tyr Ser Ile Thr Leu Gln Val Arg Leu Pro Leu Leu Thr Arg Leu
        275                 280                 285

Leu Asn Thr Gln Ile Tyr Lys Val Asp Ser Ile Ser Tyr Asn Ile Gln
    290                 295                 300

Asn Arg Glu Trp Tyr Ile Pro Leu Pro Ser His Ile Met Thr Lys Gly
305                 310                 315                 320

Ala Phe Leu Gly Gly Ala Asp Val Lys Glu Cys Ile Glu Ala Phe Ser
                325                 330                 335

Ser Tyr Ile Cys Pro Ser Asp Pro Gly Phe Val Leu Asn His Glu Met
            340                 345                 350

Glu Ser Cys Leu Ser Gly Asn Ile Ser Gln Cys Pro Arg Thr Thr Val
        355                 360                 365

Thr Ser Asp Ile Val Pro Arg Tyr Ala Phe Val Asn Gly Gly Val Val
    370                 375                 380

Ala Asn Cys Ile Thr Thr Thr Cys Thr Cys Asn Gly Ile Gly Asn Arg
385                 390                 395                 400

Ile Asn Gln Pro Pro Asp Gln Gly Val Lys Ile Ile Thr His Lys Glu
                405                 410                 415

Cys Asn Thr Ile Gly Ile Asn Gly Met Leu Phe Asn Thr Asn Lys Glu
            420                 425                 430

Gly Thr Leu Ala Phe Tyr Thr Pro Asp Asp Ile Thr Leu Asn Asn Ser
        435                 440                 445

Val Ala Leu Asp Pro Ile Asp Ile Ser Ile Glu Leu Asn Lys Ala Lys
    450                 455                 460

Ser Asp Leu Glu Glu Ser Lys Glu Trp Ile Arg Arg Ser Asn Gln Lys
465                 470                 475                 480

Leu Asp Ser Ile Gly Ser Trp His Gln Ser Ser Thr Thr Ile Ile Val
                485                 490                 495

Ile Leu Ile Met Met Ile Ile Leu Phe Ile Ile Asn Ile Thr Ile Ile
            500                 505                 510

Thr Ile Ala Ile Lys Tyr Tyr Arg Ile Gln Lys Arg Asn Arg Val Asp
        515                 520                 525

Gln Asn Asp Lys Pro Tyr Val Leu Thr Asn Lys
    530                 535
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<210> SEQ ID NO 14
<211> LENGTH: 572
<212> TYPE: PRT
<213> ORGANISM: Human parainfluenza virus 3

<400> SEQUENCE: 14

Met Glu Tyr Trp Lys His Thr Asn His Gly Lys Asp Ala Gly Asn Glu
1 5 10 15

Leu Glu Thr Ser Thr Ala Thr His Gly Asn Lys Leu Thr Asn Lys Ile
20 25 30

Thr Tyr Ile Leu Trp Thr Ile Thr Leu Val Leu Leu Ser Ile Val Phe
35 40 45

Ile Ile Val Leu Thr Asn Ser Ile Lys Ser Glu Lys Ala Arg Glu Ser
50 55 60

Leu Leu Gln Asp Ile Asn Asn Glu Phe Met Glu Val Thr Glu Lys Ile
65 70 75 80

Gln Val Ala Ser Asp Asn Thr Asn Asp Leu Ile Gln Ser Gly Val Asn
85 90 95

Thr Arg Leu Leu Thr Ile Gln Ser His Val Gln Asn Tyr Ile Pro Ile
100 105 110

Ser Leu Thr Gln Gln Ile Ser Asp Leu Arg Lys Phe Ile Ser Glu Ile
115 120 125

Thr Ile Arg Asn Asp Asn Gln Glu Val Pro Pro Gln Arg Ile Thr His
130 135 140

Asp Val Gly Ile Lys Pro Leu Asn Pro Asp Asp Phe Trp Arg Cys Thr
145 150 155 160

Ser Gly Leu Pro Ser Leu Met Lys Thr Pro Lys Ile Arg Leu Met Pro
165 170 175

Gly Pro Gly Leu Leu Ala Met Pro Thr Thr Val Asp Gly Cys Val Arg
180 185 190

Thr Pro Ser Leu Val Ile Asn Asp Leu Ile Tyr Ala Tyr Thr Ser Asn
195 200 205

Leu Ile Thr Arg Gly Cys Gln Asp Ile Gly Lys Ser Tyr Gln Val Leu
210 215 220

Gln Ile Gly Ile Ile Thr Val Asn Ser Asp Leu Val Pro Asp Leu Asn
225 230 235 240

Pro Arg Ile Ser His Thr Phe Asn Ile Asn Asp Asn Arg Lys Ser Cys
245 250 255

Ser Leu Ala Leu Leu Asn Thr Asp Val Tyr Gln Leu Cys Ser Thr Pro
260 265 270

Lys Val Asp Glu Arg Ser Asp Tyr Ala Ser Ser Gly Ile Glu Asp Ile
275 280 285

Val Leu Asp Ile Val Asn Tyr Asp Gly Ser Ile Ser Thr Thr Arg Phe
290 295 300

Lys Asn Asn Asn Ile Ser Phe Asp Gln Pro Tyr Ala Ala Leu Tyr Pro
305 310 315 320

Ser Val Gly Pro Gly Ile Tyr Tyr Lys Gly Lys Ile Ile Phe Leu Gly
325 330 335

Tyr Gly Gly Leu Glu His Pro Ile Asn Glu Asn Ala Ile Cys Asn Thr
340 345 350

Thr Gly Cys Pro Gly Lys Thr Gln Arg Asp Cys Asn Gln Ala Ser His
355 360 365

Ser Pro Trp Phe Ser Asp Arg Arg Met Val Asn Ser Ile Ile Val Val
370 375 380

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Asp Lys Gly Leu Asn Ser Val Pro Lys Leu Lys Val Trp Thr Ile Ser
385                 390                 395                 400

Met Arg Gln Asn Tyr Trp Gly Ser Glu Gly Arg Leu Leu Leu Leu Gly
                405                 410                 415

Asn Lys Ile Tyr Ile Tyr Thr Arg Ser Thr Ser Trp His Ser Lys Leu
            420                 425                 430

Gln Leu Gly Ile Ile Asp Ile Thr Asp Tyr Ser Asp Ile Arg Ile Lys
        435                 440                 445

Trp Thr Trp His Asn Val Leu Ser Arg Pro Gly Asn Asn Glu Cys Pro
    450                 455                 460

Trp Gly His Ser Cys Pro Asp Gly Cys Ile Thr Gly Val Tyr Thr Asp
465                 470                 475                 480

Ala Tyr Pro Leu Asn Pro Thr Gly Ser Ile Val Ser Ser Val Ile Leu
                485                 490                 495

Asp Ser Gln Lys Ser Arg Val Asn Pro Val Ile Thr Tyr Ser Thr Ala
            500                 505                 510

Thr Glu Arg Val Asn Glu Leu Ala Ile Arg Asn Lys Thr Leu Ser Ala
        515                 520                 525

Gly Tyr Thr Thr Thr Ser Cys Ile Thr His Tyr Asn Lys Gly Tyr Cys
    530                 535                 540

Phe His Ile Val Glu Ile Asn His Lys Ser Leu Asn Thr Phe Gln Pro
545                 550                 555                 560

Met Leu Phe Lys Thr Glu Ile Pro Lys Ser Cys Ser
                565                 570


<210> SEQ ID NO 15
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 15

Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1               5                   10                  15

Asp Thr Thr Gly
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<210> SEQ ID NO 16
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 16

Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1               5                   10                  15

His Ser


<210> SEQ ID NO 17
<211> LENGTH: 24
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 17

Met Leu Gly Ser Asn Ser Gly Gln Arg Val Val Phe Thr Ile Leu Leu
1               5                   10                  15
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Leu Leu Val Ala Pro Ala Tyr Ser
20

<210> SEQ ID NO 18
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 18

Met Lys Cys Leu Leu Tyr Leu Ala Phe Leu Phe Ile Gly Val Asn Cys
1 5 10 15

Ala

<210> SEQ ID NO 19
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 19

Met Trp Leu Val Ser Leu Ala Ile Val Thr Ala Cys Ala Gly Ala
1 5 10 15

<210> SEQ ID NO 20
<211> LENGTH: 4062
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Middle East respiratory syndrome coronavirus

<400> SEQUENCE: 20

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gataaaactt ggcctaggcc aattgatgtt tctaaggctg acggtattat atacctcaa 180

ggccgtacat attctaacat aactatcact tatcaaggtc tttttcccta tcagggagac 240

catggtgata tgtatgttta ctctgcagga catgctacag gcacaactcc acaaaagttg 300

tttgtagcta actattctca ggacgtcaaa cagtttgcta atgggtttgt cgtccgtata 360

ggagcagctg ccaattccac tggcactgtt attattagcc catctaccag cgctactata 420

cgaaaaattt accctgcttt tatgctgggt tcttcagttg gtaatttctc agatggtaaa 480

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tttgccacct tgcctgttta tgatactatt aagtattatt ctatcattcc tcacagtatt 900

cgttctatcc aaagtgatag aaaagcttgg gctgccttct acgtatataa acttcaaccg 960

ttaactttcc tgttggattt ttctgttgat ggttatatac gcagagctat agactgtggt 1020

tttaatgatt tgtcacaact ccactgctca tatgaatcct tcgatgttga atctggagtt 1080

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cgtttggttt ttaccaattg caattataat cttaccaaat tgctttcact tttttctgtg 1260

aatgatttta cttgtagtca aatatctcca gcagcaattg ctagcaactg ttattcttca 1320

ctgattttgg attatttttc atacccactt agtatgaaat ccgatctcag tgttagttct 1380

gctggtccaa tatcccagtt taattataaa cagtcctttt ctaatcccac atgtttgatc 1440

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aatcaatact caccctgtgt atccattgtc ccatccactg tgtgggaaga cggtgattat 1620

tataggaaac aactatctcc acttgaaggt ggtggctggc ttgttgctag tggctcaact 1680

gttgccatga ctgagcaatt acagatgggc tttggtatta cagttcaata tggtacagac 1740

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cctactaatt gtatagcccc tgttaatggc tactttatta aaactaataa cactaggatt 3540

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aatgttagca ccagtatacc taattttggt tctctaacac agattaatac tacattactc 3780

gatcttacct acgagatgtt gtctcttcaa caagttgtta aagcccttaa tgagtcttac 3840

atagacctta aagagcttgg caattatact tattacaaca aatggccgtg gtacatttgg 3900

cttggtttca ttgctgggct tgttgcctta gctctatgcg tcttcttcat actgtgctgc 3960

actggttgtg gcacaaactg tatgggaaaa cttaagtgta atcgttgttg tgatagatac 4020

gaggaatacg acctcgagcc gcataaggtt catgttcact aa 4062

<210> SEQ ID NO 21
<211> LENGTH: 4062
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 21

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gataaaactt ggcctaggcc aattgatgtt tctaaggctg acggtattat ataccctcaa 180

ggccgtacat attctaacat aactatcact tatcaaggtc tttttcccta tcagggagac 240

catggtgata tgtatgttta ctctgcagga catgctacag gcacaactcc acaaaagttg 300

tttgtagcta actattctca ggacgtcaaa cagtttgcta atgggtttgt cgtccgtata 360

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cgaaaaattt accctgcttt tatgctgggt tcttcagttg gtaatttctc agatggtaaa 480

atgggccgct tcttcaatca tactctagtt cttttgcccg atggatgtgg cactttactt 540

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cgtttggttt ttaccaattg caattataat cttaccaaat tgctttcact tttttctgtg 1260

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gctggtccaa tatcccagtt taattataaa cagtcctttt ctaatcccac atgtttgatt 1440

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actggttgtg gcacaaactg tatgggaaaa cttaagtgta atcgttgttg tgatagatac 4020

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<210> SEQ ID NO 22
<211> LENGTH: 1845
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 22

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tccgtgcggt cggtgcctgg cgaaatgcgg ctggcctcca tcgccttcaa tcacccaatc 180

caagtggatc agctgaatag ctcgtatttc aagctgtcca tccccacgaa cttctcgttc 240

ggggtcaccc aggagtacat ccagaccaca attcagaagg tcaccgtcga ttgcaagcaa 300

tacgtgtgca acggcttcca gaagtgcgag cagctgctga gagaatacgg gcagttttgc 360

agcaagatca accaggcgct gcatggagct aacttgcgcc aggacgactc cgtgcgcaac 420

ctctttgcct ctgtgaagtc atcccagtcc tccccaatca tcccgggatt cggaggggac 480

ttcaacctga ccctcctgga gcccgtgtcg atcagcaccg gtagcagatc ggcgcgctca 540

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gctatcccct ttgcacaatc cattttctac cggctcaacg gcgtgggcat tactcaacaa 840

gtcctgtcgg agaaccagaa gttgatcgca aacaagttca atcaggccct gggggccatg 900

cagactggat tcactacgac taacgaagcg ttccagaagg tccaggacgc tgtgaacaac 960

aacgcccagg cgctctcaaa gctggcctcc gaactcagca acaccttcgg agccatcagc 1020

gcatcgatcg gtgacataat tcagcggctg gacgtgctgg agcaggacgc ccagatcgac 1080

cgcctcatca acggacggct gaccaccttg aatgccttcg tggcacaaca gctggtccgg 1140

agcgaatcag cggcactttc cgcccaactc gccaaggaca aagtcaacga atgcgtgaag 1200

gcccagtcca agaggtccgg tttctgcggt caaggaaccc atattgtgtc cttcgtcgtg 1260

aacgcgccca acggtctgta ctttatgcac gtcggctact acccgagcaa tcatatcgaa 1320

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gtgacctacc agaacatctc caccaatttg ccgccgccgc tgctcggaaa cagcaccgga 1560

attgatttcc aagatgaact ggacgaattc ttcaagaacg tgtccacttc cattcccaac 1620

ttcggaagcc tgacacagat caacaccacc cttctcgacc tgacctacga gatgctgagc 1680

cttcaacaag tggtcaaggc cctgaacgag agctacatcg acctgaagga gctgggcaac 1740

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<210> SEQ ID NO 23
<211> LENGTH: 4071
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 23

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cagacctttt tcgacaagac ctggcccaga cccatcgacg tgtccaaggc cgacggcatc 180

atctatccac aaggccggac ctacagcaac atcaccatta cctaccaggg cctgttccca 240

tatcaaggcg accacggcga tatgtacgtg tactctgccg gccacgccac cggcaccaca 300

ccccagaaac tgttcgtggc caactacagc caggacgtga agcagttcgc caacggcttc 360

gtcgtgcgga ttggcgccgc tgccaatagc accggcacag tgatcatcag ccccagcacc 420

agcgccacca tccggaagat ctaccccgcc ttcatgctgg gcagctccgt gggcaatttc 480

agcgacggca agatgggccg gttcttcaac cacaccctgg tgctgctgcc cgatggctgt 540

ggcacactgc tgagagcctt ctactgcatc ctggaaccca gaagcggcaa ccactgccct 600

gccggcaata gctacaccag cttcgccacc taccacacac ccgccaccga ttgctccgac 660

ggcaactaca accggaacgc cagcctgaac agcttcaaag agtacttcaa cctgcggaac 720

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aacatgttcc agtttgccac cctgcccgtg tacgacacca tcaagtacta cagcatcatc 900

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aagctgcagc ccctgacctt cctgctggac ttcagcgtgg acggctacat cagacgggcc 1020

atcgactgcg gcttcaacga cctgagccag ctgcactgct cctacgagag cttcgacgtg 1080

gaaagcggcg tgtacagcgt gtccagcttc gaggccaagc ctagcggcag cgtggtggaa 1140

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tacaacttca agcggctggt gttcaccaac tgcaattaca acctgaccaa gctgctgagc 1260

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agcgtgtcct ccgccggacc catcagccag ttcaactaca agcagagctt cagcaaccct 1440

acctgcctga ttctggccac cgtgccccac aatctgacca ccatcaccaa gcccctgaag 1500

tacagctaca tcaacaagtg cagcagactg ctgtccgacg accggaccga agtgccccag 1560

ctcgtgaacg ccaaccagta cagcccctgc gtgtccatcg tgcccagcac cgtgtgggag 1620

gacggcgact actacagaaa gcagctgagc cccctggaag gcggcggatg gctggtggct 1680

tctggaagca cagtggccat gaccgagcag ctgcagatgg gctttggcat caccgtgcag 1740

tacggcaccg acaccaacag cgtgtgcccc aagctggaat tcgccaatga caccaagatc 1800

gccagccagc tgggaaactg cgtggaatac tccctgtatg gcgtgtccgg acggggcgtg 1860

ttccagaatt gcacagcagt gggagtgcgg cagcagagat tcgtgtacga tgcctaccag 1920

aacctcgtgg gctactacag cgacgacggc aattactact gcctgcgggc ctgtgtgtcc 1980

gtgcccgtgt ccgtgatcta cgacaaagag acaaagaccc acgccacact gttcggctcc 2040

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gtggcctgcg agcacatcag ctccaccatg agccagtact cccgctccac ccggtccatg 2100

ctgaagcgga gagatagcac ctacggcccc ctgcagacac ctgtgggatg tgtgctgggc 2160

ctcgtgaaca gctccctgtt tgtggaagat tgcaagctgc ccctgggcca gagcctgtgt 2220

gccctgccag ataccctag caccctgacc cctagaagcg tgcgctctgt gcccggcgaa 2280

atgcggctgg cctctatcgc cttcaatcac cccatccagg tggaccagct gaactccagc 2340

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atcgccaaca agtttaacca ggcactgggc gccatgcaga ccggcttcac caccaccaac 3060

gaggccttca gaaaggtgca ggacgccgtg aacaacaacg cccaggctct gagcaagctg 3120

gcctccgagc tgagcaatac cttcggcgcc atcagcgcct ccatcggcga catcatccag 3180

cggctggacg tgctggaaca ggacgcccag atcgaccggc tgatcaacgg cagactgacc 3240

accctgaacg ccttcgtggc acagcagctc gtgcggagcg aatctgccgc tctgtctgct 3300

cagctggcca aggacaaagt gaacgagtgc gtgaaggccc agtccaagcg gagcggcttt 3360

tgtggccagg gcacccacat cgtgtccttc gtcgtgaatg cccccaacgg cctgtacttt 3420

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gagttcttca agaacgtgtc cacctccatc cccaacttcg gcagcctgac ccagatcaac 3780

accactctgc tggacctgac ctacgagatg ctgtccctgc aacaggtcgt gaaagccctg 3840

aacgagagct acatcgacct gaaagagctg gggaactaca cctactacaa caagtggcct 3900

tggtacattt ggctgggctt tatcgccggc ctggtggccc tggccctgtg cgtgttcttc 3960

atcctgtgct gcaccggctg cggcaccaat tgcatgggca agctgaaatg caaccggtgc 4020

tgcgacagat acgaggaata cgacctggaa cctcacaaag tgcatgtgca c 4071

<210> SEQ ID NO 24
<211> LENGTH: 1353
<212> TYPE: PRT
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Middle East respiratory syndrome coronavirus

<400> SEQUENCE: 24

Met Ile His Ser Val Phe Leu Leu Met Phe Leu Leu Thr Pro Thr Glu

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1               5                  10                  15

Ser Tyr Val Asp Val Gly Pro Asp Ser Val Lys Ser Ala Cys Ile Glu
            20                  25                  30

Val Asp Ile Gln Gln Thr Phe Phe Asp Lys Thr Trp Pro Arg Pro Ile
        35                  40                  45

Asp Val Ser Lys Ala Asp Gly Ile Ile Tyr Pro Gln Gly Arg Thr Tyr
    50                  55                  60

Ser Asn Ile Thr Ile Thr Tyr Gln Gly Leu Phe Pro Tyr Gln Gly Asp
65                  70                  75                  80

His Gly Asp Met Tyr Val Tyr Ser Ala Gly His Ala Thr Gly Thr Thr
                85                  90                  95

Pro Gln Lys Leu Phe Val Ala Asn Tyr Ser Gln Asp Val Lys Gln Phe
            100                 105                 110

Ala Asn Gly Phe Val Val Arg Ile Gly Ala Ala Ala Asn Ser Thr Gly
        115                 120                 125

Thr Val Ile Ile Ser Pro Ser Thr Ser Ala Thr Ile Arg Lys Ile Tyr
    130                 135                 140

Pro Ala Phe Met Leu Gly Ser Ser Val Gly Asn Phe Ser Asp Gly Lys
145                 150                 155                 160

Met Gly Arg Phe Phe Asn His Thr Leu Val Leu Leu Pro Asp Gly Cys
                165                 170                 175

Gly Thr Leu Leu Arg Ala Phe Tyr Cys Ile Leu Glu Pro Arg Ser Gly
            180                 185                 190

Asn His Cys Pro Ala Gly Asn Ser Tyr Thr Ser Phe Ala Thr Tyr His
        195                 200                 205

Thr Pro Ala Thr Asp Cys Ser Asp Gly Asn Tyr Asn Arg Asn Ala Ser
    210                 215                 220

Leu Asn Ser Phe Lys Glu Tyr Phe Asn Leu Arg Asn Cys Thr Phe Met
225                 230                 235                 240

Tyr Thr Tyr Asn Ile Thr Glu Asp Glu Ile Leu Glu Trp Phe Gly Ile
                245                 250                 255

Thr Gln Thr Ala Gln Gly Val His Leu Phe Ser Ser Arg Tyr Val Asp
            260                 265                 270

Leu Tyr Gly Gly Asn Met Phe Gln Phe Ala Thr Leu Pro Val Tyr Asp
        275                 280                 285

Thr Ile Lys Tyr Tyr Ser Ile Ile Pro His Ser Ile Arg Ser Ile Gln
    290                 295                 300

Ser Asp Arg Lys Ala Trp Ala Ala Phe Tyr Val Tyr Lys Leu Gln Pro
305                 310                 315                 320

Leu Thr Phe Leu Leu Asp Phe Ser Val Asp Gly Tyr Ile Arg Arg Ala
                325                 330                 335

Ile Asp Cys Gly Phe Asn Asp Leu Ser Gln Leu His Cys Ser Tyr Glu
            340                 345                 350

Ser Phe Asp Val Glu Ser Gly Val Tyr Ser Val Ser Ser Phe Glu Ala
        355                 360                 365

Lys Pro Ser Gly Ser Val Val Glu Gln Ala Glu Gly Val Glu Cys Asp
    370                 375                 380

Phe Ser Pro Leu Leu Ser Gly Thr Pro Pro Gln Val Tyr Asn Phe Lys
385                 390                 395                 400

Arg Leu Val Phe Thr Asn Cys Asn Tyr Asn Leu Thr Lys Leu Leu Ser
                405                 410                 415

Leu Phe Ser Val Asn Asp Phe Thr Cys Ser Gln Ile Ser Pro Ala Ala
            420                 425                 430
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Ile Ala Ser Asn Cys Tyr Ser Ser Leu Ile Leu Asp Tyr Phe Ser Tyr
        435                 440                 445

Pro Leu Ser Met Lys Ser Asp Leu Ser Val Ser Ser Ala Gly Pro Ile
    450                 455                 460

Ser Gln Phe Asn Tyr Lys Gln Ser Phe Ser Asn Pro Thr Cys Leu Ile
465                 470                 475                 480

Leu Ala Thr Val Pro His Asn Leu Thr Thr Ile Thr Lys Pro Leu Lys
                485                 490                 495

Tyr Ser Tyr Ile Asn Lys Cys Ser Arg Leu Leu Ser Asp Asp Arg Thr
            500                 505                 510

Glu Val Pro Gln Leu Val Asn Ala Asn Gln Tyr Ser Pro Cys Val Ser
        515                 520                 525

Ile Val Pro Ser Thr Val Trp Glu Asp Gly Asp Tyr Tyr Arg Lys Gln
    530                 535                 540

Leu Ser Pro Leu Glu Gly Gly Gly Trp Leu Val Ala Ser Gly Ser Thr
545                 550                 555                 560

Val Ala Met Thr Glu Gln Leu Gln Met Gly Phe Gly Ile Thr Val Gln
                565                 570                 575

Tyr Gly Thr Asp Thr Asn Ser Val Cys Pro Lys Leu Glu Phe Ala Asn
            580                 585                 590

Asp Thr Lys Ile Ala Ser Gln Leu Gly Asn Cys Val Glu Tyr Ser Leu
        595                 600                 605

Tyr Gly Val Ser Gly Arg Gly Val Phe Gln Asn Cys Thr Ala Val Gly
    610                 615                 620

Val Arg Gln Gln Arg Phe Val Tyr Asp Ala Tyr Gln Asn Leu Val Gly
625                 630                 635                 640

Tyr Tyr Ser Asp Asp Gly Asn Tyr Tyr Cys Leu Arg Ala Cys Val Ser
                645                 650                 655

Val Pro Val Ser Val Ile Tyr Asp Lys Glu Thr Lys Thr His Ala Thr
            660                 665                 670

Leu Phe Gly Ser Val Ala Cys Glu His Ile Ser Ser Thr Met Ser Gln
        675                 680                 685

Tyr Ser Arg Ser Thr Arg Ser Met Leu Lys Arg Arg Asp Ser Thr Tyr
    690                 695                 700

Gly Pro Leu Gln Thr Pro Val Gly Cys Val Leu Gly Leu Val Asn Ser
705                 710                 715                 720

Ser Leu Phe Val Glu Asp Cys Lys Leu Pro Leu Gly Gln Ser Leu Cys
                725                 730                 735

Ala Leu Pro Asp Thr Pro Ser Thr Leu Thr Pro Arg Ser Val Arg Ser
            740                 745                 750

Val Pro Gly Glu Met Arg Leu Ala Ser Ile Ala Phe Asn His Pro Ile
        755                 760                 765

Gln Val Asp Gln Leu Asn Ser Ser Tyr Phe Lys Leu Ser Ile Pro Thr
    770                 775                 780

Asn Phe Ser Phe Gly Val Thr Gln Glu Tyr Ile Gln Thr Thr Ile Gln
785                 790                 795                 800

Lys Val Thr Val Asp Cys Lys Gln Tyr Val Cys Asn Gly Phe Gln Lys
                805                 810                 815

Cys Glu Gln Leu Leu Arg Glu Tyr Gly Gln Phe Cys Ser Lys Ile Asn
            820                 825                 830

Gln Ala Leu His Gly Ala Asn Leu Arg Gln Asp Asp Ser Val Arg Asn
        835                 840                 845
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Leu Phe Ala Ser Val Lys Ser Ser Gln Ser Ser Pro Ile Ile Pro Gly
    850                 855                 860

Phe Gly Gly Asp Phe Asn Leu Thr Leu Leu Glu Pro Val Ser Ile Ser
865                 870                 875                 880

Thr Gly Ser Arg Ser Ala Arg Ser Ala Ile Glu Asp Leu Leu Phe Asp
                885                 890                 895

Lys Val Thr Ile Ala Asp Pro Gly Tyr Met Gln Gly Tyr Asp Asp Cys
            900                 905                 910

Met Gln Gln Gly Pro Ala Ser Ala Arg Asp Leu Ile Cys Ala Gln Tyr
        915                 920                 925

Val Ala Gly Tyr Lys Val Leu Pro Pro Leu Met Asp Val Asn Met Glu
    930                 935                 940

Ala Ala Tyr Thr Ser Ser Leu Leu Gly Ser Ile Ala Gly Val Gly Trp
945                 950                 955                 960

Thr Ala Gly Leu Ser Ser Phe Ala Ala Ile Pro Phe Ala Gln Ser Ile
                965                 970                 975

Phe Tyr Arg Leu Asn Gly Val Gly Ile Thr Gln Gln Val Leu Ser Glu
            980                 985                 990

Asn Gln Lys Leu Ile Ala Asn Lys  Phe Asn Gln Ala Leu  Gly Ala Met
        995                 1000                1005

Gln Thr  Gly Phe Thr Thr Thr  Asn Glu Ala Phe Arg  Lys Val Gln
    1010                1015                1020

Asp Ala  Val Asn Asn Asn Ala  Gln Ala Leu Ser Lys  Leu Ala Ser
    1025                1030                1035

Glu Leu  Ser Asn Thr Phe Gly  Ala Ile Ser Ala Ser  Ile Gly Asp
    1040                1045                1050

Ile Ile  Gln Arg Leu Asp Val  Leu Glu Gln Asp Ala  Gln Ile Asp
    1055                1060                1065

Arg Leu  Ile Asn Gly Arg Leu  Thr Thr Leu Asn Ala  Phe Val Ala
    1070                1075                1080

Gln Gln  Leu Val Arg Ser Glu  Ser Ala Ala Leu Ser  Ala Gln Leu
    1085                1090                1095

Ala Lys  Asp Lys Val Asn Glu  Cys Val Lys Ala Gln  Ser Lys Arg
    1100                1105                1110

Ser Gly  Phe Cys Gly Gln Gly  Thr His Ile Val Ser  Phe Val Val
    1115                1120                1125

Asn Ala  Pro Asn Gly Leu Tyr  Phe Met His Val Gly  Tyr Tyr Pro
    1130                1135                1140

Ser Asn  His Ile Glu Val Val  Ser Ala Tyr Gly Leu  Cys Asp Ala
    1145                1150                1155

Ala Asn  Pro Thr Asn Cys Ile  Ala Pro Val Asn Gly  Tyr Phe Ile
    1160                1165                1170

Lys Thr  Asn Asn Thr Arg Ile  Val Asp Glu Trp Ser  Tyr Thr Gly
    1175                1180                1185

Ser Ser  Phe Tyr Ala Pro Glu  Pro Ile Thr Ser Leu  Asn Thr Lys
    1190                1195                1200

Tyr Val  Ala Pro Gln Val Thr  Tyr Gln Asn Ile Ser  Thr Asn Leu
    1205                1210                1215

Pro Pro  Pro Leu Leu Gly Asn  Ser Thr Gly Ile Asp  Phe Gln Asp
    1220                1225                1230

Glu Leu  Asp Glu Phe Phe Lys  Asn Val Ser Thr Ser  Ile Pro Asn
    1235                1240                1245

Phe Gly  Ser Leu Thr Gln Ile  Asn Thr Thr Leu Leu  Asp Leu Thr
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    1250                1255                1260

Tyr Glu  Met Leu Ser Leu Gln  Gln Val Val Lys Ala  Leu Asn Glu
    1265                1270                1275

Ser Tyr  Ile Asp Leu Lys Glu  Leu Gly Asn Tyr Thr  Tyr Tyr Asn
    1280                1285                1290

Lys Trp  Pro Trp Tyr Ile Trp  Leu Gly Phe Ile Ala  Gly Leu Val
    1295                1300                1305

Ala Leu  Ala Leu Cys Val Phe  Phe Ile Leu Cys Cys  Thr Gly Cys
    1310                1315                1320

Gly Thr  Asn Cys Met Gly Lys  Leu Lys Cys Asn Arg  Cys Cys Asp
    1325                1330                1335

Arg Tyr  Glu Glu Tyr Asp Leu  Glu Pro His Lys Val  His Val His
    1340                1345                1350


<210> SEQ ID NO 25
<211> LENGTH: 1353
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 25

Met Ile His Ser Val Phe Leu Leu Met Phe Leu Leu Thr Pro Thr Glu
1               5                   10                  15

Ser Tyr Val Asp Val Gly Pro Asp Ser Val Lys Ser Ala Cys Ile Glu
            20                  25                  30

Val Asp Ile Gln Gln Thr Phe Phe Asp Lys Thr Trp Pro Arg Pro Ile
        35                  40                  45

Asp Val Ser Lys Ala Asp Gly Ile Ile Tyr Pro Gln Gly Arg Thr Tyr
    50                  55                  60

Ser Asn Ile Thr Ile Thr Tyr Gln Gly Leu Phe Pro Tyr Gln Gly Asp
65                  70                  75                  80

His Gly Asp Met Tyr Val Tyr Ser Ala Gly His Ala Thr Gly Thr Thr
                85                  90                  95

Pro Gln Lys Leu Phe Val Ala Asn Tyr Ser Gln Asp Val Lys Gln Phe
            100                 105                 110

Ala Asn Gly Phe Val Val Arg Ile Gly Ala Ala Ala Asn Ser Thr Gly
        115                 120                 125

Thr Val Ile Ile Ser Pro Ser Thr Ser Ala Thr Ile Arg Lys Ile Tyr
    130                 135                 140

Pro Ala Phe Met Leu Gly Ser Ser Val Gly Asn Phe Ser Asp Gly Lys
145                 150                 155                 160

Met Gly Arg Phe Phe Asn His Thr Leu Val Leu Leu Pro Asp Gly Cys
                165                 170                 175

Gly Thr Leu Leu Arg Ala Phe Tyr Cys Ile Leu Glu Pro Arg Ser Gly
            180                 185                 190

Asn His Cys Pro Ala Gly Asn Ser Tyr Thr Ser Phe Ala Thr Tyr His
        195                 200                 205

Thr Pro Ala Thr Asp Cys Ser Asp Gly Asn Tyr Asn Arg Asn Ala Ser
    210                 215                 220

Leu Asn Ser Phe Lys Glu Tyr Phe Asn Leu Arg Asn Cys Thr Phe Met
225                 230                 235                 240

Tyr Thr Tyr Asn Ile Thr Glu Asp Glu Ile Leu Glu Trp Phe Gly Ile
                245                 250                 255

Thr Gln Thr Ala Gln Gly Val His Leu Phe Ser Ser Arg Tyr Val Asp
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            260                 265                 270

Leu Tyr Gly Gly Asn Met Phe Gln Phe Ala Thr Leu Pro Val Tyr Asp
        275                 280                 285

Thr Ile Lys Tyr Tyr Ser Ile Ile Pro His Ser Ile Arg Ser Ile Gln
    290                 295                 300

Ser Asp Arg Lys Ala Trp Ala Ala Phe Tyr Val Tyr Lys Leu Gln Pro
305                 310                 315                 320

Leu Thr Phe Leu Leu Asp Phe Ser Val Asp Gly Tyr Ile Arg Arg Ala
                325                 330                 335

Ile Asp Cys Gly Phe Asn Asp Leu Ser Gln Leu His Cys Ser Tyr Glu
            340                 345                 350

Ser Phe Asp Val Glu Ser Gly Val Tyr Ser Val Ser Ser Phe Glu Ala
        355                 360                 365

Lys Pro Ser Gly Ser Val Val Glu Gln Ala Glu Gly Val Glu Cys Asp
    370                 375                 380

Phe Ser Pro Leu Leu Ser Gly Thr Pro Pro Gln Val Tyr Asn Phe Lys
385                 390                 395                 400

Arg Leu Val Phe Thr Asn Cys Asn Tyr Asn Leu Thr Lys Leu Leu Ser
                405                 410                 415

Leu Phe Ser Val Asn Asp Phe Thr Cys Ser Gln Ile Ser Pro Ala Ala
            420                 425                 430

Ile Ala Ser Asn Cys Tyr Ser Ser Leu Ile Leu Asp Tyr Phe Ser Tyr
        435                 440                 445

Pro Leu Ser Met Lys Ser Asp Leu Ser Val Ser Ser Ala Gly Pro Ile
    450                 455                 460

Ser Gln Phe Asn Tyr Lys Gln Ser Phe Ser Asn Pro Thr Cys Leu Ile
465                 470                 475                 480

Leu Ala Thr Val Pro His Asn Leu Thr Thr Ile Thr Lys Pro Leu Lys
                485                 490                 495

Tyr Ser Tyr Ile Asn Lys Cys Ser Arg Leu Leu Ser Asp Asp Arg Thr
            500                 505                 510

Glu Val Pro Gln Leu Val Asn Ala Asn Gln Tyr Ser Pro Cys Val Ser
        515                 520                 525

Ile Val Pro Ser Thr Val Trp Glu Asp Gly Asp Tyr Tyr Arg Lys Gln
    530                 535                 540

Leu Ser Pro Leu Glu Gly Gly Gly Trp Leu Val Ala Ser Gly Ser Thr
545                 550                 555                 560

Val Ala Met Thr Glu Gln Leu Gln Met Gly Phe Gly Ile Thr Val Gln
                565                 570                 575

Tyr Gly Thr Asp Thr Asn Ser Val Cys Pro Lys Leu Glu Phe Ala Asn
            580                 585                 590

Asp Thr Lys Ile Ala Ser Gln Leu Gly Asn Cys Val Glu Tyr Ser Leu
        595                 600                 605

Tyr Gly Val Ser Gly Arg Gly Val Phe Gln Asn Cys Thr Ala Val Gly
    610                 615                 620

Val Arg Gln Gln Arg Phe Val Tyr Asp Ala Tyr Gln Asn Leu Val Gly
625                 630                 635                 640

Tyr Tyr Ser Asp Asp Gly Asn Tyr Tyr Cys Leu Arg Ala Cys Val Ser
                645                 650                 655

Val Pro Val Ser Val Ile Tyr Asp Lys Glu Thr Lys Thr His Ala Thr
            660                 665                 670

Leu Phe Gly Ser Val Ala Cys Glu His Ile Ser Ser Thr Met Ser Gln
        675                 680                 685
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Tyr Ser Arg Ser Thr Arg Ser Met Leu Lys Arg Arg Asp Ser Thr Tyr
    690                 695                 700

Gly Pro Leu Gln Thr Pro Val Gly Cys Val Leu Gly Leu Val Asn Ser
705                 710                 715                 720

Ser Leu Phe Val Glu Asp Cys Lys Leu Pro Leu Gly Gln Ser Leu Cys
                725                 730                 735

Ala Leu Pro Asp Thr Pro Ser Thr Leu Thr Pro Arg Ser Val Arg Ser
            740                 745                 750

Val Pro Gly Glu Met Arg Leu Ala Ser Ile Ala Phe Asn His Pro Ile
        755                 760                 765

Gln Val Asp Gln Leu Asn Ser Ser Tyr Phe Lys Leu Ser Ile Pro Thr
    770                 775                 780

Asn Phe Ser Phe Gly Val Thr Gln Glu Tyr Ile Gln Thr Thr Ile Gln
785                 790                 795                 800

Lys Val Thr Val Asp Cys Lys Gln Tyr Val Cys Asn Gly Phe Gln Lys
                805                 810                 815

Cys Glu Gln Leu Leu Arg Glu Tyr Gly Gln Phe Cys Ser Lys Ile Asn
            820                 825                 830

Gln Ala Leu His Gly Ala Asn Leu Arg Gln Asp Asp Ser Val Arg Asn
        835                 840                 845

Leu Phe Ala Ser Val Lys Ser Ser Gln Ser Ser Pro Ile Ile Pro Gly
    850                 855                 860

Phe Gly Gly Asp Phe Asn Leu Thr Leu Leu Glu Pro Val Ser Ile Ser
865                 870                 875                 880

Thr Gly Ser Arg Ser Ala Arg Ser Ala Ile Glu Asp Leu Leu Phe Asp
                885                 890                 895

Lys Val Thr Ile Ala Asp Pro Gly Tyr Met Gln Gly Tyr Asp Asp Cys
            900                 905                 910

Met Gln Gln Gly Pro Ala Ser Ala Arg Asp Leu Ile Cys Ala Gln Tyr
        915                 920                 925

Val Ala Gly Tyr Lys Val Leu Pro Pro Leu Met Asp Val Asn Met Glu
    930                 935                 940

Ala Ala Tyr Thr Ser Ser Leu Leu Gly Ser Ile Ala Gly Val Gly Trp
945                 950                 955                 960

Thr Ala Gly Leu Ser Ser Phe Ala Ala Ile Pro Phe Ala Gln Ser Ile
                965                 970                 975

Phe Tyr Arg Leu Asn Gly Val Gly Ile Thr Gln Gln Val Leu Ser Glu
            980                 985                 990

Asn Gln Lys Leu Ile Ala Asn Lys  Phe Asn Gln Ala Leu  Gly Ala Met
        995                 1000                1005

Gln Thr  Gly Phe Thr Thr Thr  Asn Glu Ala Phe Gln  Lys Val Gln
    1010                1015                1020

Asp Ala  Val Asn Asn Asn Ala  Gln Ala Leu Ser Lys  Leu Ala Ser
    1025                1030                1035

Glu Leu  Ser Asn Thr Phe Gly  Ala Ile Ser Ala Ser  Ile Gly Asp
    1040                1045                1050

Ile Ile  Gln Arg Leu Asp Val  Leu Glu Gln Asp Ala  Gln Ile Asp
    1055                1060                1065

Arg Leu  Ile Asn Gly Arg Leu  Thr Thr Leu Asn Ala  Phe Val Ala
    1070                1075                1080

Gln Gln  Leu Val Arg Ser Glu  Ser Ala Ala Leu Ser  Ala Gln Leu
    1085                1090                1095
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Ala Lys  Asp Lys Val Asn Glu  Cys Val Lys Ala Gln  Ser Lys Arg
    1100                1105                1110

Ser Gly  Phe Cys Gly Gln Gly  Thr His Ile Val Ser  Phe Val Val
    1115                1120                1125

Asn Ala  Pro Asn Gly Leu Tyr  Phe Met His Val Gly  Tyr Tyr Pro
    1130                1135                1140

Ser Asn  His Ile Glu Val Val  Ser Ala Tyr Gly Leu  Cys Asp Ala
    1145                1150                1155

Ala Asn  Pro Thr Asn Cys Ile  Ala Pro Val Asn Gly  Tyr Phe Ile
    1160                1165                1170

Lys Thr  Asn Asn Thr Arg Ile  Val Asp Glu Trp Ser  Tyr Thr Gly
    1175                1180                1185

Ser Ser  Phe Tyr Ala Pro Glu  Pro Ile Thr Ser Leu  Asn Thr Lys
    1190                1195                1200

Tyr Val  Ala Pro Gln Val Thr  Tyr Gln Asn Ile Ser  Thr Asn Leu
    1205                1210                1215

Pro Pro  Pro Leu Leu Gly Asn  Ser Thr Gly Ile Asp  Phe Gln Asp
    1220                1225                1230

Glu Leu  Asp Glu Phe Phe Lys  Asn Val Ser Thr Ser  Ile Pro Asn
    1235                1240                1245

Phe Gly  Ser Leu Thr Gln Ile  Asn Thr Thr Leu Leu  Asp Leu Thr
    1250                1255                1260

Tyr Glu  Met Leu Ser Leu Gln  Gln Val Val Lys Ala  Leu Asn Glu
    1265                1270                1275

Ser Tyr  Ile Asp Leu Lys Glu  Leu Gly Asn Tyr Thr  Tyr Tyr Asn
    1280                1285                1290

Lys Trp  Pro Trp Tyr Ile Trp  Leu Gly Phe Ile Ala  Gly Leu Val
    1295                1300                1305

Ala Leu  Ala Leu Cys Val Phe  Phe Ile Leu Cys Cys  Thr Gly Cys
    1310                1315                1320

Gly Thr  Asn Cys Met Gly Lys  Leu Lys Cys Asn Arg  Cys Cys Asp
    1325                1330                1335

Arg Tyr  Glu Glu Tyr Asp Leu  Glu Pro His Lys Val  His Val His
    1340                1345                1350


<210> SEQ ID NO 26
<211> LENGTH: 615
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 26

Met Ile His Ser Val Phe Leu Leu Met Phe Leu Leu Thr Pro Thr Glu
1               5                  10                  15

Ser Asp Cys Lys Leu Pro Leu Gly Gln Ser Leu Cys Ala Leu Pro Asp
            20                  25                  30

Thr Pro Ser Thr Leu Thr Pro Arg Ser Val Arg Ser Val Pro Gly Glu
        35                  40                  45

Met Arg Leu Ala Ser Ile Ala Phe Asn His Pro Ile Gln Val Asp Gln
    50                  55                  60

Leu Asn Ser Ser Tyr Phe Lys Leu Ser Ile Pro Thr Asn Phe Ser Phe
65                  70                  75                  80

Gly Val Thr Gln Glu Tyr Ile Gln Thr Thr Ile Gln Lys Val Thr Val
                85                  90                  95
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Asp Cys Lys Gln Tyr Val Cys Asn Gly Phe Gln Lys Cys Glu Gln Leu
            100                 105                 110

Leu Arg Glu Tyr Gly Gln Phe Cys Ser Lys Ile Asn Gln Ala Leu His
        115                 120                 125

Gly Ala Asn Leu Arg Gln Asp Asp Ser Val Arg Asn Leu Phe Ala Ser
    130                 135                 140

Val Lys Ser Ser Gln Ser Ser Pro Ile Ile Pro Gly Phe Gly Gly Asp
145                 150                 155                 160

Phe Asn Leu Thr Leu Leu Glu Pro Val Ser Ile Ser Thr Gly Ser Arg
                165                 170                 175

Ser Ala Arg Ser Ala Ile Glu Asp Leu Leu Phe Asp Lys Val Thr Ile
            180                 185                 190

Ala Asp Pro Gly Tyr Met Gln Gly Tyr Asp Asp Cys Met Gln Gln Gly
        195                 200                 205

Pro Ala Ser Ala Arg Asp Leu Ile Cys Ala Gln Tyr Val Ala Gly Tyr
    210                 215                 220

Lys Val Leu Pro Pro Leu Met Asp Val Asn Met Glu Ala Ala Tyr Thr
225                 230                 235                 240

Ser Ser Leu Leu Gly Ser Ile Ala Gly Val Gly Trp Thr Ala Gly Leu
                245                 250                 255

Ser Ser Phe Ala Ala Ile Pro Phe Ala Gln Ser Ile Phe Tyr Arg Leu
            260                 265                 270

Asn Gly Val Gly Ile Thr Gln Gln Val Leu Ser Glu Asn Gln Lys Leu
        275                 280                 285

Ile Ala Asn Lys Phe Asn Gln Ala Leu Gly Ala Met Gln Thr Gly Phe
    290                 295                 300

Thr Thr Thr Asn Glu Ala Phe Gln Lys Val Gln Asp Ala Val Asn Asn
305                 310                 315                 320

Asn Ala Gln Ala Leu Ser Lys Leu Ala Ser Glu Leu Ser Asn Thr Phe
                325                 330                 335

Gly Ala Ile Ser Ala Ser Ile Gly Asp Ile Ile Gln Arg Leu Asp Val
            340                 345                 350

Leu Glu Gln Asp Ala Gln Ile Asp Arg Leu Ile Asn Gly Arg Leu Thr
        355                 360                 365

Thr Leu Asn Ala Phe Val Ala Gln Gln Leu Val Arg Ser Glu Ser Ala
    370                 375                 380

Ala Leu Ser Ala Gln Leu Ala Lys Asp Lys Val Asn Glu Cys Val Lys
385                 390                 395                 400

Ala Gln Ser Lys Arg Ser Gly Phe Cys Gly Gln Gly Thr His Ile Val
                405                 410                 415

Ser Phe Val Val Asn Ala Pro Asn Gly Leu Tyr Phe Met His Val Gly
            420                 425                 430

Tyr Tyr Pro Ser Asn His Ile Glu Val Val Ser Ala Tyr Gly Leu Cys
        435                 440                 445

Asp Ala Ala Asn Pro Thr Asn Cys Ile Ala Pro Val Asn Gly Tyr Phe
    450                 455                 460

Ile Lys Thr Asn Asn Thr Arg Ile Val Asp Glu Trp Ser Tyr Thr Gly
465                 470                 475                 480

Ser Ser Phe Tyr Ala Pro Glu Pro Ile Thr Ser Leu Asn Thr Lys Tyr
                485                 490                 495

Val Ala Pro Gln Val Thr Tyr Gln Asn Ile Ser Thr Asn Leu Pro Pro
            500                 505                 510

Pro Leu Leu Gly Asn Ser Thr Gly Ile Asp Phe Gln Asp Glu Leu Asp
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        515                 520                 525

Glu Phe Phe Lys Asn Val Ser Thr Ser Ile Pro Asn Phe Gly Ser Leu
    530                 535                 540

Thr Gln Ile Asn Thr Thr Leu Leu Asp Leu Thr Tyr Glu Met Leu Ser
545                 550                 555                 560

Leu Gln Gln Val Val Lys Ala Leu Asn Glu Ser Tyr Ile Asp Leu Lys
                565                 570                 575

Glu Leu Gly Asn Tyr Thr Tyr Tyr Asn Lys Trp Pro Asp Lys Ile Glu
            580                 585                 590

Glu Ile Leu Ser Lys Ile Tyr His Ile Glu Asn Glu Ile Ala Arg Ile
        595                 600                 605

Lys Lys Leu Ile Gly Glu Ala
    610                 615


<210> SEQ ID NO 27
<211> LENGTH: 1353
<212> TYPE: PRT
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Middle East respiratory syndrome coronavirus

<400> SEQUENCE: 27

Met Ile His Ser Val Phe Leu Leu Met Phe Leu Leu Thr Pro Thr Glu
1               5                   10                  15

Ser Tyr Val Asp Val Gly Pro Asp Ser Val Lys Ser Ala Cys Ile Glu
            20                  25                  30

Val Asp Ile Gln Gln Thr Phe Phe Asp Lys Thr Trp Pro Arg Pro Ile
        35                  40                  45

Asp Val Ser Lys Ala Asp Gly Ile Ile Tyr Pro Gln Gly Arg Thr Tyr
    50                  55                  60

Ser Asn Ile Thr Ile Thr Tyr Gln Gly Leu Phe Pro Tyr Gln Gly Asp
65                  70                  75                  80

His Gly Asp Met Tyr Val Tyr Ser Ala Gly His Ala Thr Gly Thr Thr
                85                  90                  95

Pro Gln Lys Leu Phe Val Ala Asn Tyr Ser Gln Asp Val Lys Gln Phe
            100                 105                 110

Ala Asn Gly Phe Val Val Arg Ile Gly Ala Ala Ala Asn Ser Thr Gly
        115                 120                 125

Thr Val Ile Ile Ser Pro Ser Thr Ser Ala Thr Ile Arg Lys Ile Tyr
    130                 135                 140

Pro Ala Phe Met Leu Gly Ser Ser Val Gly Asn Phe Ser Asp Gly Lys
145                 150                 155                 160

Met Gly Arg Phe Phe Asn His Thr Leu Val Leu Leu Pro Asp Gly Cys
                165                 170                 175

Gly Thr Leu Leu Arg Ala Phe Tyr Cys Ile Leu Glu Pro Arg Ser Gly
            180                 185                 190

Asn His Cys Pro Ala Gly Asn Ser Tyr Thr Ser Phe Ala Thr Tyr His
        195                 200                 205

Thr Pro Ala Thr Asp Cys Ser Asp Gly Asn Tyr Asn Arg Asn Ala Ser
    210                 215                 220

Leu Asn Ser Phe Lys Glu Tyr Phe Asn Leu Arg Asn Cys Thr Phe Met
225                 230                 235                 240

Tyr Thr Tyr Asn Ile Thr Glu Asp Glu Ile Leu Glu Trp Phe Gly Ile
                245                 250                 255

Thr Gln Thr Ala Gln Gly Val His Leu Phe Ser Ser Arg Tyr Val Asp
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            260                 265                 270

Leu Tyr Gly Gly Asn Met Phe Gln Phe Ala Thr Leu Pro Val Tyr Asp
        275                 280                 285

Thr Ile Lys Tyr Tyr Ser Ile Ile Pro His Ser Ile Arg Ser Ile Gln
    290                 295                 300

Ser Asp Arg Lys Ala Trp Ala Ala Phe Tyr Val Tyr Lys Leu Gln Pro
305                 310                 315                 320

Leu Thr Phe Leu Leu Asp Phe Ser Val Asp Gly Tyr Ile Arg Arg Ala
                325                 330                 335

Ile Asp Cys Gly Phe Asn Asp Leu Ser Gln Leu His Cys Ser Tyr Glu
            340                 345                 350

Ser Phe Asp Val Glu Ser Gly Val Tyr Ser Val Ser Ser Phe Glu Ala
        355                 360                 365

Lys Pro Ser Gly Ser Val Val Glu Gln Ala Glu Gly Val Glu Cys Asp
    370                 375                 380

Phe Ser Pro Leu Leu Ser Gly Thr Pro Pro Gln Val Tyr Asn Phe Lys
385                 390                 395                 400

Arg Leu Val Phe Thr Asn Cys Asn Tyr Asn Leu Thr Lys Leu Leu Ser
                405                 410                 415

Leu Phe Ser Val Asn Asp Phe Thr Cys Ser Gln Ile Ser Pro Ala Ala
            420                 425                 430

Ile Ala Ser Asn Cys Tyr Ser Ser Leu Ile Leu Asp Tyr Phe Ser Tyr
        435                 440                 445

Pro Leu Ser Met Lys Ser Asp Leu Ser Val Ser Ser Ala Gly Pro Ile
    450                 455                 460

Ser Gln Phe Asn Tyr Lys Gln Ser Phe Ser Asn Pro Thr Cys Leu Ile
465                 470                 475                 480

Leu Ala Thr Val Pro His Asn Leu Thr Thr Ile Thr Lys Pro Leu Lys
                485                 490                 495

Tyr Ser Tyr Ile Asn Lys Cys Ser Arg Leu Leu Ser Asp Asp Arg Thr
            500                 505                 510

Glu Val Pro Gln Leu Val Asn Ala Asn Gln Tyr Ser Pro Cys Val Ser
        515                 520                 525

Ile Val Pro Ser Thr Val Trp Glu Asp Gly Asp Tyr Tyr Arg Lys Gln
    530                 535                 540

Leu Ser Pro Leu Glu Gly Gly Gly Trp Leu Val Ala Ser Gly Ser Thr
545                 550                 555                 560

Val Ala Met Thr Glu Gln Leu Gln Met Gly Phe Gly Ile Thr Val Gln
                565                 570                 575

Tyr Gly Thr Asp Thr Asn Ser Val Cys Pro Lys Leu Glu Phe Ala Asn
            580                 585                 590

Asp Thr Lys Ile Ala Ser Gln Leu Gly Asn Cys Val Glu Tyr Ser Leu
        595                 600                 605

Tyr Gly Val Ser Gly Arg Gly Val Phe Gln Asn Cys Thr Ala Val Gly
    610                 615                 620

Val Arg Gln Gln Arg Phe Val Tyr Asp Ala Tyr Gln Asn Leu Val Gly
625                 630                 635                 640

Tyr Tyr Ser Asp Asp Gly Asn Tyr Tyr Cys Leu Arg Ala Cys Val Ser
                645                 650                 655

Val Pro Val Ser Val Ile Tyr Asp Lys Glu Thr Lys Thr His Ala Thr
            660                 665                 670

Leu Phe Gly Ser Val Ala Cys Glu His Ile Ser Ser Thr Met Ser Gln
        675                 680                 685
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Tyr Ser Arg Ser Thr Arg Ser Met Leu Lys Arg Arg Asp Ser Thr Tyr
    690                 695                 700

Gly Pro Leu Gln Thr Pro Val Gly Cys Val Leu Gly Leu Val Asn Ser
705                 710                 715                 720

Ser Leu Phe Val Glu Asp Cys Lys Leu Pro Leu Gly Gln Ser Leu Cys
                725                 730                 735

Ala Leu Pro Asp Thr Pro Ser Thr Leu Thr Pro Arg Ser Val Arg Ser
            740                 745                 750

Val Pro Gly Glu Met Arg Leu Ala Ser Ile Ala Phe Asn His Pro Ile
        755                 760                 765

Gln Val Asp Gln Leu Asn Ser Ser Tyr Phe Lys Leu Ser Ile Pro Thr
    770                 775                 780

Asn Phe Ser Phe Gly Val Thr Gln Glu Tyr Ile Gln Thr Thr Ile Gln
785                 790                 795                 800

Lys Val Thr Val Asp Cys Lys Gln Tyr Val Cys Asn Gly Phe Gln Lys
                805                 810                 815

Cys Glu Gln Leu Leu Arg Glu Tyr Gly Gln Phe Cys Ser Lys Ile Asn
            820                 825                 830

Gln Ala Leu His Gly Ala Asn Leu Arg Gln Asp Asp Ser Val Arg Asn
        835                 840                 845

Leu Phe Ala Ser Val Lys Ser Ser Gln Ser Ser Pro Ile Ile Pro Gly
    850                 855                 860

Phe Gly Gly Asp Phe Asn Leu Thr Leu Leu Glu Pro Val Ser Ile Ser
865                 870                 875                 880

Thr Gly Ser Arg Ser Ala Arg Ser Ala Ile Glu Asp Leu Leu Phe Asp
                885                 890                 895

Lys Val Thr Ile Ala Asp Pro Gly Tyr Met Gln Gly Tyr Asp Asp Cys
            900                 905                 910

Met Gln Gln Gly Pro Ala Ser Ala Arg Asp Leu Ile Cys Ala Gln Tyr
        915                 920                 925

Val Ala Gly Tyr Lys Val Leu Pro Pro Leu Met Asp Val Asn Met Glu
    930                 935                 940

Ala Ala Tyr Thr Ser Ser Leu Leu Gly Ser Ile Ala Gly Val Gly Trp
945                 950                 955                 960

Thr Ala Gly Leu Ser Ser Phe Ala Ala Ile Pro Phe Ala Gln Ser Ile
                965                 970                 975

Phe Tyr Arg Leu Asn Gly Val Gly Ile Thr Gln Gln Val Leu Ser Glu
            980                 985                 990

Asn Gln Lys Leu Ile Ala Asn Lys  Phe Asn Gln Ala Leu  Gly Ala Met
        995                 1000                1005

Gln Thr  Gly Phe Thr Thr Thr  Asn Glu Ala Phe Arg  Lys Val Gln
    1010                1015                1020

Asp Ala  Val Asn Asn Asn Ala  Gln Ala Leu Ser Lys  Leu Ala Ser
    1025                1030                1035

Glu Leu  Ser Asn Thr Phe Gly  Ala Ile Ser Ala Ser  Ile Gly Asp
    1040                1045                1050

Ile Ile  Gln Arg Leu Asp Val  Leu Glu Gln Asp Ala  Gln Ile Asp
    1055                1060                1065

Arg Leu  Ile Asn Gly Arg Leu  Thr Thr Leu Asn Ala  Phe Val Ala
    1070                1075                1080

Gln Gln  Leu Val Arg Ser Glu  Ser Ala Ala Leu Ser  Ala Gln Leu
    1085                1090                1095
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Ala Lys  Asp Lys Val Asn Glu  Cys Val Lys Ala Gln  Ser Lys Arg
    1100                 1105                 1110

Ser Gly  Phe Cys Gly Gln Gly  Thr His Ile Val Ser  Phe Val Val
    1115                 1120                 1125

Asn Ala  Pro Asn Gly Leu Tyr  Phe Met His Val Gly  Tyr Tyr Pro
    1130                 1135                 1140

Ser Asn  His Ile Glu Val Val  Ser Ala Tyr Gly Leu  Cys Asp Ala
    1145                 1150                 1155

Ala Asn  Pro Thr Asn Cys Ile  Ala Pro Val Asn Gly  Tyr Phe Ile
    1160                 1165                 1170

Lys Thr  Asn Asn Thr Arg Ile  Val Asp Glu Trp Ser  Tyr Thr Gly
    1175                 1180                 1185

Ser Ser  Phe Tyr Ala Pro Glu  Pro Ile Thr Ser Leu  Asn Thr Lys
    1190                 1195                 1200

Tyr Val  Ala Pro His Val Thr  Tyr Gln Asn Ile Ser  Thr Asn Leu
    1205                 1210                 1215

Pro Pro  Pro Leu Leu Gly Asn  Ser Thr Gly Ile Asp  Phe Gln Asp
    1220                 1225                 1230

Glu Leu  Asp Glu Phe Phe Lys  Asn Val Ser Thr Ser  Ile Pro Asn
    1235                 1240                 1245

Phe Gly  Ser Leu Thr Gln Ile  Asn Thr Thr Leu Leu  Asp Leu Thr
    1250                 1255                 1260

Tyr Glu  Met Leu Ser Leu Gln  Gln Val Val Lys Ala  Leu Asn Glu
    1265                 1270                 1275

Ser Tyr  Ile Asp Leu Lys Glu  Leu Gly Asn Tyr Thr  Tyr Tyr Asn
    1280                 1285                 1290

Lys Trp  Pro Trp Tyr Ile Trp  Leu Gly Phe Ile Ala  Gly Leu Val
    1295                 1300                 1305

Ala Leu  Ala Leu Cys Val Phe  Phe Ile Leu Cys Cys  Thr Gly Cys
    1310                 1315                 1320

Gly Thr  Asn Cys Met Gly Lys  Leu Lys Cys Asn Arg  Cys Cys Asp
    1325                 1330                 1335

Arg Tyr  Glu Glu Tyr Asp Leu  Glu Pro His Lys Val  His Val His
    1340                 1345                 1350


<210> SEQ ID NO 28
<211> LENGTH: 1353
<212> TYPE: PRT
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Middle East respiratory syndrome coronavirus

<400> SEQUENCE: 28

Met Ile His Ser Val Phe Leu Leu Met Phe Leu Leu Thr Pro Thr Glu
1               5                  10                  15

Ser Tyr Val Asp Val Gly Pro Asp Ser Val Lys Ser Ala Cys Ile Glu
            20                  25                  30

Val Asp Ile Gln Gln Thr Phe Phe Asp Lys Thr Trp Pro Arg Pro Ile
        35                  40                  45

Asp Val Ser Lys Ala Asp Gly Ile Ile Tyr Pro Gln Gly Arg Thr Tyr
    50                  55                  60

Ser Asn Ile Thr Ile Thr Tyr Gln Gly Leu Phe Pro Tyr Gln Gly Asp
65                  70                  75                  80

His Gly Asp Met Tyr Val Tyr Ser Ala Gly His Ala Thr Gly Thr Thr
                85                  90                  95
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Pro Gln Lys Leu Phe Val Ala Asn Tyr Ser Gln Asp Val Lys Gln Phe
            100                 105                 110

Ala Asn Gly Phe Val Val Arg Ile Gly Ala Ala Ala Asn Ser Thr Gly
        115                 120                 125

Thr Val Ile Ile Ser Pro Ser Thr Ser Ala Thr Ile Arg Lys Ile Tyr
    130                 135                 140

Pro Ala Phe Met Leu Gly Ser Ser Val Gly Asn Phe Ser Asp Gly Lys
145                 150                 155                 160

Met Gly Arg Phe Phe Asn His Thr Leu Val Leu Leu Pro Asp Gly Cys
                165                 170                 175

Gly Thr Leu Leu Arg Ala Phe Tyr Cys Ile Leu Glu Pro Arg Ser Gly
            180                 185                 190

Asn His Cys Pro Ala Gly Asn Ser Tyr Thr Ser Phe Ala Thr Tyr His
        195                 200                 205

Thr Pro Ala Thr Asp Cys Ser Asp Gly Asn Tyr Asn Arg Asn Ala Ser
    210                 215                 220

Leu Asn Ser Phe Lys Glu Tyr Phe Asn Leu Arg Asn Cys Thr Phe Met
225                 230                 235                 240

Tyr Thr Tyr Asn Ile Thr Glu Asp Glu Ile Leu Glu Trp Phe Gly Ile
                245                 250                 255

Thr Gln Thr Ala Gln Gly Val His Leu Phe Ser Ser Arg Tyr Val Asp
            260                 265                 270

Leu Tyr Gly Gly Asn Met Phe Gln Phe Ala Thr Leu Pro Val Tyr Asp
        275                 280                 285

Thr Ile Lys Tyr Tyr Ser Ile Ile Pro His Ser Ile Arg Ser Ile Gln
    290                 295                 300

Ser Asp Arg Lys Ala Trp Ala Ala Phe Tyr Val Tyr Lys Leu Gln Pro
305                 310                 315                 320

Leu Thr Phe Leu Leu Asp Phe Ser Val Asp Gly Tyr Ile Arg Arg Ala
                325                 330                 335

Ile Asp Cys Gly Phe Asn Asp Leu Ser Gln Leu His Cys Ser Tyr Glu
            340                 345                 350

Ser Phe Asp Val Glu Ser Gly Val Tyr Ser Val Ser Ser Phe Glu Ala
        355                 360                 365

Lys Pro Ser Gly Ser Val Val Glu Gln Ala Glu Gly Val Glu Cys Asp
    370                 375                 380

Phe Ser Pro Leu Leu Ser Gly Thr Pro Pro Gln Val Tyr Asn Phe Lys
385                 390                 395                 400

Arg Leu Val Phe Thr Asn Cys Asn Tyr Asn Leu Thr Lys Leu Leu Ser
                405                 410                 415

Leu Phe Ser Val Asn Asp Phe Thr Cys Ser Gln Ile Ser Pro Ala Ala
            420                 425                 430

Ile Ala Ser Asn Cys Tyr Ser Ser Leu Ile Leu Asp Tyr Phe Ser Tyr
        435                 440                 445

Pro Leu Ser Met Lys Ser Asp Leu Ser Val Ser Ser Ala Gly Pro Ile
    450                 455                 460

Ser Gln Phe Asn Tyr Lys Gln Ser Phe Ser Asn Pro Thr Cys Leu Ile
465                 470                 475                 480

Leu Ala Thr Val Pro His Asn Leu Thr Thr Ile Thr Lys Pro Leu Lys
                485                 490                 495

Tyr Ser Tyr Ile Asn Lys Cys Ser Arg Leu Leu Ser Asp Asp Arg Thr
            500                 505                 510

Glu Val Pro Gln Leu Val Asn Ala Asn Gln Tyr Ser Pro Cys Val Ser
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        515                 520                 525

Ile Val Pro Ser Thr Val Trp Glu Asp Gly Asp Tyr Tyr Arg Lys Gln
    530                 535                 540

Leu Ser Pro Leu Glu Gly Gly Gly Trp Leu Val Ala Ser Gly Ser Thr
545                 550                 555                 560

Val Ala Met Thr Glu Gln Leu Gln Met Gly Phe Gly Ile Thr Val Gln
                565                 570                 575

Tyr Gly Thr Asp Thr Asn Ser Val Cys Pro Lys Leu Glu Phe Ala Asn
            580                 585                 590

Asp Thr Lys Ile Ala Ser Gln Leu Gly Asn Cys Val Glu Tyr Ser Leu
        595                 600                 605

Tyr Gly Val Ser Gly Arg Gly Val Phe Gln Asn Cys Thr Ala Val Gly
    610                 615                 620

Val Arg Gln Gln Arg Phe Val Tyr Asp Ala Tyr Gln Asn Leu Val Gly
625                 630                 635                 640

Tyr Tyr Ser Asp Asp Gly Asn Tyr Tyr Cys Leu Arg Ala Cys Val Ser
                645                 650                 655

Val Pro Val Ser Val Ile Tyr Asp Lys Glu Thr Lys Thr His Ala Thr
            660                 665                 670

Leu Phe Gly Ser Val Ala Cys Glu His Ile Ser Ser Thr Met Ser Gln
        675                 680                 685

Tyr Ser Arg Ser Thr Arg Ser Met Leu Lys Arg Arg Asp Ser Thr Tyr
    690                 695                 700

Gly Pro Leu Gln Thr Pro Val Gly Cys Val Leu Gly Leu Val Asn Ser
705                 710                 715                 720

Ser Leu Phe Val Glu Asp Cys Lys Leu Pro Leu Gly Gln Ser Leu Cys
                725                 730                 735

Ala Leu Pro Asp Thr Pro Ser Thr Leu Thr Pro Arg Ser Val Arg Ser
            740                 745                 750

Val Pro Gly Glu Met Arg Leu Ala Ser Ile Ala Phe Asn His Pro Ile
        755                 760                 765

Gln Val Asp Gln Leu Asn Ser Ser Tyr Phe Lys Leu Ser Ile Pro Thr
    770                 775                 780

Asn Phe Ser Phe Gly Val Thr Gln Glu Tyr Ile Gln Thr Thr Ile Gln
785                 790                 795                 800

Lys Val Thr Val Asp Cys Lys Gln Tyr Val Cys Asn Gly Phe Gln Lys
                805                 810                 815

Cys Glu Gln Leu Leu Arg Glu Tyr Gly Gln Phe Cys Ser Lys Ile Asn
            820                 825                 830

Gln Ala Leu His Gly Ala Asn Leu Arg Gln Asp Asp Ser Val Arg Asn
        835                 840                 845

Leu Phe Ala Ser Val Lys Ser Ser Gln Ser Ser Pro Ile Ile Pro Gly
    850                 855                 860

Phe Gly Gly Asp Phe Asn Leu Thr Leu Leu Glu Pro Val Ser Ile Ser
865                 870                 875                 880

Thr Gly Ser Arg Ser Ala Arg Ser Ala Ile Glu Asp Leu Leu Phe Asp
                885                 890                 895

Lys Val Thr Ile Ala Asp Pro Gly Tyr Met Gln Gly Tyr Asp Asp Cys
            900                 905                 910

Met Gln Gln Gly Pro Ala Ser Ala Arg Asp Leu Ile Cys Ala Gln Tyr
        915                 920                 925

Val Ala Gly Tyr Lys Val Leu Pro Pro Leu Met Asp Val Asn Met Glu
    930                 935                 940
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Ala Ala Tyr Thr Ser Ser Leu Leu Gly Ser Ile Ala Gly Val Gly Trp
945                 950                 955                 960

Thr Ala Gly Leu Ser Ser Phe Ala Ala Ile Pro Phe Ala Gln Ser Ile
                965                 970                 975

Phe Tyr Arg Leu Asn Gly Val Gly Ile Thr Gln Gln Val Leu Ser Glu
            980                 985                 990

Asn Gln Lys Leu Ile Ala Asn Lys  Phe Asn Gln Ala Leu  Gly Ala Met
        995                 1000                1005

Gln Thr  Gly Phe Thr Thr Thr  Asn Glu Ala Phe Arg  Lys Val Gln
    1010                1015                1020

Asp Ala  Val Asn Asn Asn Ala  Gln Ala Leu Ser Lys  Leu Ala Ser
    1025                1030                1035

Glu Leu  Ser Asn Thr Phe Gly  Ala Ile Ser Ala Ser  Ile Gly Asp
    1040                1045                1050

Ile Ile  Gln Arg Leu Asp Val  Leu Glu Gln Asp Ala  Gln Ile Asp
    1055                1060                1065

Arg Leu  Ile Asn Gly Arg Leu  Thr Thr Leu Asn Ala  Phe Val Ala
    1070                1075                1080

Gln Gln  Leu Val Arg Ser Glu  Ser Ala Ala Leu Ser  Ala Gln Leu
    1085                1090                1095

Ala Lys  Asp Lys Val Asn Glu  Cys Val Lys Ala Gln  Ser Lys Arg
    1100                1105                1110

Ser Gly  Phe Cys Gly Gln Gly  Thr His Ile Val Ser  Phe Val Val
    1115                1120                1125

Asn Ala  Pro Asn Gly Leu Tyr  Phe Met His Val Gly  Tyr Tyr Pro
    1130                1135                1140

Ser Asn  His Ile Glu Val Val  Ser Ala Tyr Gly Leu  Cys Asp Ala
    1145                1150                1155

Ala Asn  Pro Thr Asn Cys Ile  Ala Pro Val Asn Gly  Tyr Phe Ile
    1160                1165                1170

Lys Thr  Asn Asn Thr Arg Ile  Val Asp Glu Trp Ser  Tyr Thr Gly
    1175                1180                1185

Ser Ser  Phe Tyr Ala Pro Glu  Pro Ile Thr Ser Leu  Asn Thr Lys
    1190                1195                1200

Tyr Val  Ala Pro His Val Thr  Tyr Gln Asn Ile Ser  Thr Asn Leu
    1205                1210                1215

Pro Pro  Pro Leu Leu Gly Asn  Ser Thr Gly Ile Asp  Phe Gln Asp
    1220                1225                1230

Glu Leu  Asp Glu Phe Phe Lys  Asn Val Ser Thr Ser  Ile Pro Asn
    1235                1240                1245

Phe Gly  Ser Leu Thr Gln Ile  Asn Thr Thr Leu Leu  Asp Leu Thr
    1250                1255                1260

Tyr Glu  Met Leu Ser Leu Gln  Gln Val Val Lys Ala  Leu Asn Glu
    1265                1270                1275

Ser Tyr  Ile Asp Leu Lys Glu  Leu Gly Asn Tyr Thr  Tyr Tyr Asn
    1280                1285                1290

Lys Trp  Pro Trp Tyr Ile Trp  Leu Gly Phe Ile Ala  Gly Leu Val
    1295                1300                1305

Ala Leu  Ala Leu Cys Val Phe  Phe Ile Leu Cys Cys  Thr Gly Cys
    1310                1315                1320

Gly Thr  Asn Cys Met Gly Lys  Leu Lys Cys Asn Arg  Cys Cys Asp
    1325                1330                1335
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Arg Tyr  Glu Glu Tyr Asp Leu  Glu Pro His Lys Val  His Val His
    1340                1345                1350


<210> SEQ ID NO 29
<211> LENGTH: 1255
<212> TYPE: PRT
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Human SARS coronavirus

<400> SEQUENCE: 29

Met Phe Ile Phe Leu Leu Phe Leu Thr Leu Thr Ser Gly Ser Asp Leu
1               5                   10                  15

Asp Arg Cys Thr Thr Phe Asp Asp Val Gln Ala Pro Asn Tyr Thr Gln
            20                  25                  30

His Thr Ser Ser Met Arg Gly Val Tyr Tyr Pro Asp Glu Ile Phe Arg
        35                  40                  45

Ser Asp Thr Leu Tyr Leu Thr Gln Asp Leu Phe Leu Pro Phe Tyr Ser
    50                  55                  60

Asn Val Thr Gly Phe His Thr Ile Asn His Thr Phe Gly Asn Pro Val
65                  70                  75                  80

Ile Pro Phe Lys Asp Gly Ile Tyr Phe Ala Ala Thr Glu Lys Ser Asn
                85                  90                  95

Val Val Arg Gly Trp Val Phe Gly Ser Thr Met Asn Asn Lys Ser Gln
            100                 105                 110

Ser Val Ile Ile Ile Asn Asn Ser Thr Asn Val Val Ile Arg Ala Cys
        115                 120                 125

Asn Phe Glu Leu Cys Asp Asn Pro Phe Phe Ala Val Ser Lys Pro Met
    130                 135                 140

Gly Thr Gln Thr His Thr Met Ile Phe Asp Asn Ala Phe Asn Cys Thr
145                 150                 155                 160

Phe Glu Tyr Ile Ser Asp Ala Phe Ser Leu Asp Val Ser Glu Lys Ser
                165                 170                 175

Gly Asn Phe Lys His Leu Arg Glu Phe Val Phe Lys Asn Lys Asp Gly
            180                 185                 190

Phe Leu Tyr Val Tyr Lys Gly Tyr Gln Pro Ile Asp Val Val Arg Asp
        195                 200                 205

Leu Pro Ser Gly Phe Asn Thr Leu Lys Pro Ile Phe Lys Leu Pro Leu
    210                 215                 220

Gly Ile Asn Ile Thr Asn Phe Arg Ala Ile Leu Thr Ala Phe Ser Pro
225                 230                 235                 240

Ala Gln Asp Ile Trp Gly Thr Ser Ala Ala Ala Tyr Phe Val Gly Tyr
                245                 250                 255

Leu Lys Pro Thr Thr Phe Met Leu Lys Tyr Asp Glu Asn Gly Thr Ile
            260                 265                 270

Thr Asp Ala Val Asp Cys Ser Gln Asn Pro Leu Ala Glu Leu Lys Cys
        275                 280                 285

Ser Val Lys Ser Phe Glu Ile Asp Lys Gly Ile Tyr Gln Thr Ser Asn
    290                 295                 300

Phe Arg Val Val Pro Ser Gly Asp Val Val Arg Phe Pro Asn Ile Thr
305                 310                 315                 320

Asn Leu Cys Pro Phe Gly Glu Val Phe Asn Ala Thr Lys Phe Pro Ser
                325                 330                 335

Val Tyr Ala Trp Glu Arg Lys Lys Ile Ser Asn Cys Val Ala Asp Tyr
            340                 345                 350
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Ser Val Leu Tyr Asn Ser Thr Phe Phe Ser Thr Phe Lys Cys Tyr Gly
        355                 360                 365

Val Ser Ala Thr Lys Leu Asn Asp Leu Cys Phe Ser Asn Val Tyr Ala
    370                 375                 380

Asp Ser Phe Val Val Lys Gly Asp Asp Val Arg Gln Ile Ala Pro Gly
385                 390                 395                 400

Gln Thr Gly Val Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe
                405                 410                 415

Met Gly Cys Val Leu Ala Trp Asn Thr Arg Asn Ile Asp Ala Thr Ser
            420                 425                 430

Thr Gly Asn Tyr Asn Tyr Lys Tyr Arg Tyr Leu Arg His Gly Lys Leu
        435                 440                 445

Arg Pro Phe Glu Arg Asp Ile Ser Asn Val Pro Phe Ser Pro Asp Gly
    450                 455                 460

Lys Pro Cys Thr Pro Pro Ala Leu Asn Cys Tyr Trp Pro Leu Asn Asp
465                 470                 475                 480

Tyr Gly Phe Tyr Thr Thr Thr Gly Ile Gly Tyr Gln Pro Tyr Arg Val
                485                 490                 495

Val Val Leu Ser Phe Glu Leu Leu Asn Ala Pro Ala Thr Val Cys Gly
            500                 505                 510

Pro Lys Leu Ser Thr Asp Leu Ile Lys Asn Gln Cys Val Asn Phe Asn
        515                 520                 525

Phe Asn Gly Leu Thr Gly Thr Gly Val Leu Thr Pro Ser Ser Lys Arg
    530                 535                 540

Phe Gln Pro Phe Gln Gln Phe Gly Arg Asp Val Ser Asp Phe Thr Asp
545                 550                 555                 560

Ser Val Arg Asp Pro Lys Thr Ser Glu Ile Leu Asp Ile Ser Pro Cys
                565                 570                 575

Ser Phe Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Ala Ser Ser
            580                 585                 590

Glu Val Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Asp Val Ser Thr
        595                 600                 605

Ala Ile His Ala Asp Gln Leu Thr Pro Ala Trp Arg Ile Tyr Ser Thr
    610                 615                 620

Gly Asn Asn Val Phe Gln Thr Gln Ala Gly Cys Leu Ile Gly Ala Glu
625                 630                 635                 640

His Val Asp Thr Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile
                645                 650                 655

Cys Ala Ser Tyr His Thr Val Ser Leu Leu Arg Ser Thr Ser Gln Lys
            660                 665                 670

Ser Ile Val Ala Tyr Thr Met Ser Leu Gly Ala Asp Ser Ser Ile Ala
        675                 680                 685

Tyr Ser Asn Asn Thr Ile Ala Ile Pro Thr Asn Phe Ser Ile Ser Ile
    690                 695                 700

Thr Thr Glu Val Met Pro Val Ser Met Ala Lys Thr Ser Val Asp Cys
705                 710                 715                 720

Asn Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ala Asn Leu Leu Leu
                725                 730                 735

Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Ser Gly Ile
            740                 745                 750

Ala Ala Glu Gln Asp Arg Asn Thr Arg Glu Val Phe Ala Gln Val Lys
        755                 760                 765

Gln Met Tyr Lys Thr Pro Thr Leu Lys Tyr Phe Gly Gly Phe Asn Phe
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    770                 775                 780

Ser Gln Ile Leu Pro Asp Pro Leu Lys Pro Thr Lys Arg Ser Phe Ile
785                 790                 795                 800

Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Met
                805                 810                 815

Lys Gln Tyr Gly Glu Cys Leu Gly Asp Ile Asn Ala Arg Asp Leu Ile
            820                 825                 830

Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr
        835                 840                 845

Asp Asp Met Ile Ala Ala Tyr Thr Ala Ala Leu Val Ser Gly Thr Ala
    850                 855                 860

Thr Ala Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe
865                 870                 875                 880

Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn
                885                 890                 895

Val Leu Tyr Glu Asn Gln Lys Gln Ile Ala Asn Gln Phe Asn Lys Ala
            900                 905                 910

Ile Ser Gln Ile Gln Glu Ser Leu Thr Thr Thr Ser Thr Ala Leu Gly
        915                 920                 925

Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu
    930                 935                 940

Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn
945                 950                 955                 960

Asp Ile Leu Ser Arg Leu Asp Lys Val Glu Ala Glu Val Gln Ile Asp
                965                 970                 975

Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln
            980                 985                 990

Gln Leu Ile Arg Ala Ala Glu Ile  Arg Ala Ser Ala Asn  Leu Ala Ala
        995                 1000                1005

Thr Lys  Met Ser Glu Cys Val  Leu Gly Gln Ser Lys  Arg Val Asp
    1010                1015                1020

Phe Cys  Gly Lys Gly Tyr His  Leu Met Ser Phe Pro  Gln Ala Ala
    1025                1030                1035

Pro His  Gly Val Val Phe Leu  His Val Thr Tyr Val  Pro Ser Gln
    1040                1045                1050

Glu Arg  Asn Phe Thr Thr Ala  Pro Ala Ile Cys His  Glu Gly Lys
    1055                1060                1065

Ala Tyr  Phe Pro Arg Glu Gly  Val Phe Val Phe Asn  Gly Thr Ser
    1070                1075                1080

Trp Phe  Ile Thr Gln Arg Asn  Phe Phe Ser Pro Gln  Ile Ile Thr
    1085                1090                1095

Thr Asp  Asn Thr Phe Val Ser  Gly Asn Cys Asp Val  Val Ile Gly
    1100                1105                1110

Ile Ile  Asn Asn Thr Val Tyr  Asp Pro Leu Gln Pro  Glu Leu Asp
    1115                1120                1125

Ser Phe  Lys Glu Glu Leu Asp  Lys Tyr Phe Lys Asn  His Thr Ser
    1130                1135                1140

Pro Asp  Val Asp Leu Gly Asp  Ile Ser Gly Ile Asn  Ala Ser Val
    1145                1150                1155

Val Asn  Ile Gln Lys Glu Ile  Asp Arg Leu Asn Glu  Val Ala Lys
    1160                1165                1170

Asn Leu  Asn Glu Ser Leu Ile  Asp Leu Gln Glu Leu  Gly Lys Tyr
    1175                1180                1185
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Glu Gln  Tyr Ile Lys Trp Pro  Trp Tyr Val Trp Leu  Gly Phe Ile
    1190                1195                1200

Ala Gly  Leu Ile Ala Ile Val  Met Val Thr Ile Leu  Leu Cys Cys
    1205                1210                1215

Met Thr  Ser Cys Cys Ser Cys  Leu Lys Gly Ala Cys  Ser Cys Gly
    1220                1225                1230

Ser Cys  Cys Lys Phe Asp Glu  Asp Asp Ser Glu Pro  Val Leu Lys
    1235                1240                1245

Gly Val  Lys Leu His Tyr Thr
    1250                1255


<210> SEQ ID NO 30
<211> LENGTH: 1353
<212> TYPE: PRT
<213> ORGANISM: Human coronavirus

<400> SEQUENCE: 30

Met Phe Leu Ile Leu Leu Ile Ser Leu Pro Thr Ala Phe Ala Val Ile
1               5                   10                  15

Gly Asp Leu Lys Cys Thr Ser Asp Asn Ile Asn Asp Lys Asp Thr Gly
            20                  25                  30

Pro Pro Pro Ile Ser Thr Asp Thr Val Asp Val Thr Asn Gly Leu Gly
        35                  40                  45

Thr Tyr Tyr Val Leu Asp Arg Val Tyr Leu Asn Thr Thr Leu Phe Leu
    50                  55                  60

Asn Gly Tyr Tyr Pro Thr Ser Gly Ser Thr Tyr Arg Asn Met Ala Leu
65                  70                  75                  80

Lys Gly Ser Val Leu Leu Ser Arg Leu Trp Phe Lys Pro Pro Phe Leu
                85                  90                  95

Ser Asp Phe Ile Asn Gly Ile Phe Ala Lys Val Lys Asn Thr Lys Val
            100                 105                 110

Ile Lys Asp Arg Val Met Tyr Ser Glu Phe Pro Ala Ile Thr Ile Gly
        115                 120                 125

Ser Thr Phe Val Asn Thr Ser Tyr Ser Val Val Val Gln Pro Arg Thr
    130                 135                 140

Ile Asn Ser Thr Gln Asp Gly Asp Asn Lys Leu Gln Gly Leu Leu Glu
145                 150                 155                 160

Val Ser Val Cys Gln Tyr Asn Met Cys Glu Tyr Pro Gln Thr Ile Cys
                165                 170                 175

His Pro Asn Leu Gly Asn His Arg Lys Glu Leu Trp His Leu Asp Thr
            180                 185                 190

Gly Val Val Ser Cys Leu Tyr Lys Arg Asn Phe Thr Tyr Asp Val Asn
        195                 200                 205

Ala Asp Tyr Leu Tyr Phe His Phe Tyr Gln Glu Gly Gly Thr Phe Tyr
    210                 215                 220

Ala Tyr Phe Thr Asp Thr Gly Val Val Thr Lys Phe Leu Phe Asn Val
225                 230                 235                 240

Tyr Leu Gly Met Ala Leu Ser His Tyr Tyr Val Met Pro Leu Thr Cys
                245                 250                 255

Asn Ser Lys Leu Thr Leu Glu Tyr Trp Val Thr Pro Leu Thr Ser Arg
            260                 265                 270

Gln Tyr Leu Leu Ala Phe Asn Gln Asp Gly Ile Ile Phe Asn Ala Glu
        275                 280                 285

Asp Cys Met Ser Asp Phe Met Ser Glu Ile Lys Cys Lys Thr Gln Ser
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    290                 295                 300

Ile Ala Pro Pro Thr Gly Val Tyr Glu Leu Asn Gly Tyr Thr Val Gln
305                 310                 315                 320

Pro Ile Ala Asp Val Tyr Arg Arg Lys Pro Asn Leu Pro Asn Cys Asn
                325                 330                 335

Ile Glu Ala Trp Leu Asn Asp Lys Ser Val Pro Ser Pro Leu Asn Trp
            340                 345                 350

Glu Arg Lys Thr Phe Ser Asn Cys Asn Phe Asn Met Ser Ser Leu Met
        355                 360                 365

Ser Phe Ile Gln Ala Asp Ser Phe Thr Cys Asn Asn Ile Asp Ala Ala
    370                 375                 380

Lys Ile Tyr Gly Met Cys Phe Ser Ser Ile Thr Ile Asp Lys Phe Ala
385                 390                 395                 400

Ile Pro Asn Gly Arg Lys Val Asp Leu Gln Leu Gly Asn Leu Gly Tyr
                405                 410                 415

Leu Gln Ser Phe Asn Tyr Arg Ile Asp Thr Thr Ala Thr Ser Cys Gln
            420                 425                 430

Leu Tyr Tyr Asn Leu Pro Ala Ala Asn Val Ser Val Ser Arg Phe Asn
        435                 440                 445

Pro Ser Thr Trp Asn Lys Arg Phe Gly Phe Ile Glu Asp Ser Val Phe
    450                 455                 460

Lys Pro Arg Pro Ala Gly Val Leu Thr Asn His Asp Val Val Tyr Ala
465                 470                 475                 480

Gln His Cys Phe Lys Ala Pro Lys Asn Phe Cys Pro Cys Lys Leu Asn
                485                 490                 495

Gly Ser Cys Val Gly Ser Gly Pro Gly Lys Asn Asn Gly Ile Gly Thr
            500                 505                 510

Cys Pro Ala Gly Thr Asn Tyr Leu Thr Cys Asp Asn Leu Cys Thr Pro
        515                 520                 525

Asp Pro Ile Thr Phe Thr Gly Thr Tyr Lys Cys Pro Gln Thr Lys Ser
    530                 535                 540

Leu Val Gly Ile Gly Glu His Cys Ser Gly Leu Ala Val Lys Ser Asp
545                 550                 555                 560

Tyr Cys Gly Gly Asn Ser Cys Thr Cys Arg Pro Gln Ala Phe Leu Gly
                565                 570                 575

Trp Ser Ala Asp Ser Cys Leu Gln Gly Asp Lys Cys Asn Ile Phe Ala
            580                 585                 590

Asn Phe Ile Leu His Asp Val Asn Ser Gly Leu Thr Cys Ser Thr Asp
        595                 600                 605

Leu Gln Lys Ala Asn Thr Asp Ile Ile Leu Gly Val Cys Val Asn Tyr
    610                 615                 620

Asp Leu Tyr Gly Ile Leu Gly Gln Gly Ile Phe Val Glu Val Asn Ala
625                 630                 635                 640

Thr Tyr Tyr Asn Ser Trp Gln Asn Leu Leu Tyr Asp Ser Asn Gly Asn
                645                 650                 655

Leu Tyr Gly Phe Arg Asp Tyr Ile Ile Asn Arg Thr Phe Met Ile Arg
            660                 665                 670

Ser Cys Tyr Ser Gly Arg Val Ser Ala Ala Phe His Ala Asn Ser Ser
        675                 680                 685

Glu Pro Ala Leu Leu Phe Arg Asn Ile Lys Cys Asn Tyr Val Phe Asn
    690                 695                 700

Asn Ser Leu Thr Arg Gln Leu Gln Pro Ile Asn Tyr Phe Asp Ser Tyr
705                 710                 715                 720
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Leu Gly Cys Val Val Asn Ala Tyr Asn Ser Thr Ala Ile Ser Val Gln
                725                 730                 735

Thr Cys Asp Leu Thr Val Gly Ser Gly Tyr Cys Val Asp Tyr Ser Lys
            740                 745                 750

Asn Arg Arg Ser Arg Gly Ala Ile Thr Thr Gly Tyr Arg Phe Thr Asn
        755                 760                 765

Phe Glu Pro Phe Thr Val Asn Ser Val Asn Asp Ser Leu Glu Pro Val
    770                 775                 780

Gly Gly Leu Tyr Glu Ile Gln Ile Pro Ser Glu Phe Thr Ile Gly Asn
785                 790                 795                 800

Met Val Glu Phe Ile Gln Thr Ser Ser Pro Lys Val Thr Ile Asp Cys
                805                 810                 815

Ala Ala Phe Val Cys Gly Asp Tyr Ala Ala Cys Lys Ser Gln Leu Val
            820                 825                 830

Glu Tyr Gly Ser Phe Cys Asp Asn Ile Asn Ala Ile Leu Thr Glu Val
        835                 840                 845

Asn Glu Leu Leu Asp Thr Thr Gln Leu Gln Val Ala Asn Ser Leu Met
    850                 855                 860

Asn Gly Val Thr Leu Ser Thr Lys Leu Lys Asp Gly Val Asn Phe Asn
865                 870                 875                 880

Val Asp Asp Ile Asn Phe Ser Pro Val Leu Gly Cys Leu Gly Ser Glu
                885                 890                 895

Cys Ser Lys Ala Ser Ser Arg Ser Ala Ile Glu Asp Leu Leu Phe Asp
            900                 905                 910

Lys Val Lys Leu Ser Asp Val Gly Phe Val Glu Ala Tyr Asn Asn Cys
        915                 920                 925

Thr Gly Gly Ala Glu Ile Arg Asp Leu Ile Cys Val Gln Ser Tyr Lys
    930                 935                 940

Gly Ile Lys Val Leu Pro Pro Leu Leu Ser Glu Asn Gln Ile Ser Gly
945                 950                 955                 960

Tyr Thr Leu Ala Ala Thr Ser Ala Ser Leu Phe Pro Pro Trp Thr Ala
                965                 970                 975

Ala Ala Gly Val Pro Phe Tyr Leu Asn Val Gln Tyr Arg Ile Asn Gly
            980                 985                 990

Leu Gly Val Thr Met Asp Val Leu  Ser Gln Asn Gln Lys  Leu Ile Ala
        995                 1000                1005

Asn Ala  Phe Asn Asn Ala Leu  Tyr Ala Ile Gln Glu  Gly Phe Asp
    1010                1015                1020

Ala Thr  Asn Ser Ala Leu Val  Lys Ile Gln Ala Val  Val Asn Ala
    1025                1030                1035

Asn Ala  Glu Ala Leu Asn Asn  Leu Leu Gln Gln Leu  Ser Asn Arg
    1040                1045                1050

Phe Gly  Ala Ile Ser Ala Ser  Leu Gln Glu Ile Leu  Ser Arg Leu
    1055                1060                1065

Asp Ala  Leu Glu Ala Glu Ala  Gln Ile Asp Arg Leu  Ile Asn Gly
    1070                1075                1080

Arg Leu  Thr Ala Leu Asn Ala  Tyr Val Ser Gln Gln  Leu Ser Asp
    1085                1090                1095

Ser Thr  Leu Val Lys Phe Ser  Ala Ala Gln Ala Met  Glu Lys Val
    1100                1105                1110

Asn Glu  Cys Val Lys Ser Gln  Ser Ser Arg Ile Asn  Phe Cys Gly
    1115                1120                1125
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Asn Gly  Asn His Ile Ile Ser  Leu Val Gln Asn Ala  Pro Tyr Gly
    1130                1135                1140

Leu Tyr  Phe Ile His Phe Ser  Tyr Val Pro Thr Lys  Tyr Val Thr
    1145                1150                1155

Ala Arg  Val Ser Pro Gly Leu  Cys Ile Ala Gly Asp  Arg Gly Ile
    1160                1165                1170

Ala Pro  Lys Ser Gly Tyr Phe  Val Asn Val Asn Asn  Thr Trp Met
    1175                1180                1185

Tyr Thr  Gly Ser Gly Tyr Tyr  Tyr Pro Glu Pro Ile  Thr Glu Asn
    1190                1195                1200

Asn Val  Val Val Met Ser Thr  Cys Ala Val Asn Tyr  Thr Lys Ala
    1205                1210                1215

Pro Tyr  Val Met Leu Asn Thr  Ser Ile Pro Asn Leu  Pro Asp Phe
    1220                1225                1230

Lys Glu  Glu Leu Asp Gln Trp  Phe Lys Asn Gln Thr  Ser Val Ala
    1235                1240                1245

Pro Asp  Leu Ser Leu Asp Tyr  Ile Asn Val Thr Phe  Leu Asp Leu
    1250                1255                1260

Gln Val  Glu Met Asn Arg Leu  Gln Glu Ala Ile Lys  Val Leu Asn
    1265                1270                1275

Gln Ser  Tyr Ile Asn Leu Lys  Asp Ile Gly Thr Tyr  Glu Tyr Tyr
    1280                1285                1290

Val Lys  Trp Pro Trp Tyr Val  Trp Leu Leu Ile Cys  Leu Ala Gly
    1295                1300                1305

Val Ala  Met Leu Val Leu Leu  Phe Phe Ile Cys Cys  Cys Thr Gly
    1310                1315                1320

Cys Gly  Thr Ser Cys Phe Lys  Lys Cys Gly Gly Cys  Cys Asp Asp
    1325                1330                1335

Tyr Thr  Gly Tyr Gln Glu Leu  Val Ile Lys Thr Ser  His Asp Asp
    1340                1345                1350


<210> SEQ ID NO 31
<211> LENGTH: 1351
<212> TYPE: PRT
<213> ORGANISM: Human coronavirus

<400> SEQUENCE: 31

Met Phe Leu Ile Ile Phe Ile Leu Pro Thr Thr Leu Ala Val Ile Gly
1               5                  10                  15

Asp Phe Asn Cys Thr Asn Ser Phe Ile Asn Asp Tyr Asn Lys Thr Ile
            20                  25                  30

Pro Arg Ile Ser Glu Asp Val Val Asp Val Ser Leu Gly Leu Gly Thr
        35                  40                  45

Tyr Tyr Val Leu Asn Arg Val Tyr Leu Asn Thr Thr Leu Leu Phe Thr
    50                  55                  60

Gly Tyr Phe Pro Lys Ser Gly Ala Asn Phe Arg Asp Leu Ala Leu Lys
65                  70                  75                  80

Gly Ser Ile Tyr Leu Ser Thr Leu Trp Tyr Lys Pro Pro Phe Leu Ser
                85                  90                  95

Asp Phe Asn Asn Gly Ile Phe Ser Lys Val Lys Asn Thr Lys Leu Tyr
            100                 105                 110

Val Asn Asn Thr Leu Tyr Ser Glu Phe Ser Thr Ile Val Ile Gly Ser
        115                 120                 125

Val Phe Val Asn Thr Ser Tyr Thr Ile Val Val Gln Pro His Asn Gly
    130                 135                 140
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Ile Leu Glu Ile Thr Ala Cys Gln Tyr Thr Met Cys Glu Tyr Pro His
145                 150                 155                 160

Thr Val Cys Lys Ser Lys Gly Ser Ile Arg Asn Glu Ser Trp His Ile
                165                 170                 175

Asp Ser Ser Glu Pro Leu Cys Leu Phe Lys Lys Asn Phe Thr Tyr Asn
            180                 185                 190

Val Ser Ala Asp Trp Leu Tyr Phe His Phe Tyr Gln Glu Arg Gly Val
        195                 200                 205

Phe Tyr Ala Tyr Tyr Ala Asp Val Gly Met Pro Thr Thr Phe Leu Phe
    210                 215                 220

Ser Leu Tyr Leu Gly Thr Ile Leu Ser His Tyr Tyr Val Met Pro Leu
225                 230                 235                 240

Thr Cys Asn Ala Ile Ser Ser Asn Thr Asp Asn Glu Thr Leu Glu Tyr
                245                 250                 255

Trp Val Thr Pro Leu Ser Arg Arg Gln Tyr Leu Leu Asn Phe Asp Glu
            260                 265                 270

His Gly Val Ile Thr Asn Ala Val Asp Cys Ser Ser Ser Phe Leu Ser
        275                 280                 285

Glu Ile Gln Cys Lys Thr Gln Ser Phe Ala Pro Asn Thr Gly Val Tyr
    290                 295                 300

Asp Leu Ser Gly Phe Thr Val Lys Pro Val Ala Thr Val Tyr Arg Arg
305                 310                 315                 320

Ile Pro Asn Leu Pro Asp Cys Asp Ile Asp Asn Trp Leu Asn Asn Val
                325                 330                 335

Ser Val Pro Ser Pro Leu Asn Trp Glu Arg Arg Ile Phe Ser Asn Cys
            340                 345                 350

Asn Phe Asn Leu Ser Thr Leu Leu Arg Leu Val His Val Asp Ser Phe
        355                 360                 365

Ser Cys Asn Asn Leu Asp Lys Ser Lys Ile Phe Gly Ser Cys Phe Asn
    370                 375                 380

Ser Ile Thr Val Asp Lys Phe Ala Ile Pro Asn Arg Arg Arg Asp Asp
385                 390                 395                 400

Leu Gln Leu Gly Ser Ser Gly Phe Leu Gln Ser Ser Asn Tyr Lys Ile
                405                 410                 415

Asp Ile Ser Ser Ser Ser Cys Gln Leu Tyr Tyr Ser Leu Pro Leu Val
            420                 425                 430

Asn Val Thr Ile Asn Asn Phe Asn Pro Ser Ser Trp Asn Arg Arg Tyr
        435                 440                 445

Gly Phe Gly Ser Phe Asn Leu Ser Ser Tyr Asp Val Val Tyr Ser Asp
    450                 455                 460

His Cys Phe Ser Val Asn Ser Asp Phe Cys Pro Cys Ala Asp Pro Ser
465                 470                 475                 480

Val Val Asn Ser Cys Ala Lys Ser Lys Pro Pro Ser Ala Ile Cys Pro
                485                 490                 495

Ala Gly Thr Lys Tyr Arg His Cys Asp Leu Asp Thr Thr Leu Tyr Val
            500                 505                 510

Lys Asn Trp Cys Arg Cys Ser Cys Leu Pro Asp Pro Ile Ser Thr Tyr
        515                 520                 525

Ser Pro Asn Thr Cys Pro Gln Lys Lys Val Val Val Gly Ile Gly Glu
    530                 535                 540

His Cys Pro Gly Leu Gly Ile Asn Glu Glu Lys Cys Gly Thr Gln Leu
545                 550                 555                 560
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Asn His Ser Ser Cys Phe Cys Ser Pro Asp Ala Phe Leu Gly Trp Ser
                565                 570                 575

Phe Asp Ser Cys Ile Ser Asn Asn Arg Cys Asn Ile Phe Ser Asn Phe
            580                 585                 590

Ile Phe Asn Gly Ile Asn Ser Gly Thr Thr Cys Ser Asn Asp Leu Leu
        595                 600                 605

Tyr Ser Asn Thr Glu Ile Ser Thr Gly Val Cys Val Asn Tyr Asp Leu
    610                 615                 620

Tyr Gly Ile Thr Gly Gln Gly Ile Phe Lys Glu Val Ser Ala Ala Tyr
625                 630                 635                 640

Tyr Asn Asn Trp Gln Asn Leu Leu Tyr Asp Ser Asn Gly Asn Ile Ile
                645                 650                 655

Gly Phe Lys Asp Phe Leu Thr Asn Lys Thr Tyr Thr Ile Leu Pro Cys
            660                 665                 670

Tyr Ser Gly Arg Val Ser Ala Ala Phe Tyr Gln Asn Ser Ser Ser Pro
        675                 680                 685

Ala Leu Leu Tyr Arg Asn Leu Lys Cys Ser Tyr Val Leu Asn Asn Ile
    690                 695                 700

Ser Phe Ile Ser Gln Pro Phe Tyr Phe Asp Ser Tyr Leu Gly Cys Val
705                 710                 715                 720

Leu Asn Ala Val Asn Leu Thr Ser Tyr Ser Val Ser Ser Cys Asp Leu
                725                 730                 735

Arg Met Gly Ser Gly Phe Cys Ile Asp Tyr Ala Leu Pro Ser Ser Arg
            740                 745                 750

Arg Lys Arg Arg Gly Ile Ser Ser Pro Tyr Arg Phe Val Thr Phe Glu
        755                 760                 765

Pro Phe Asn Val Ser Phe Val Asn Asp Ser Val Glu Thr Val Gly Gly
    770                 775                 780

Leu Phe Glu Ile Gln Ile Pro Thr Asn Phe Thr Ile Ala Gly His Glu
785                 790                 795                 800

Glu Phe Ile Gln Thr Ser Ser Pro Lys Val Thr Ile Asp Cys Ser Ala
                805                 810                 815

Phe Val Cys Ser Asn Tyr Ala Ala Cys His Asp Leu Leu Ser Glu Tyr
            820                 825                 830

Gly Thr Phe Cys Asp Asn Ile Asn Ser Ile Leu Asn Glu Val Asn Asp
        835                 840                 845

Leu Leu Asp Ile Thr Gln Leu Gln Val Ala Asn Ala Leu Met Gln Gly
    850                 855                 860

Val Thr Leu Ser Ser Asn Leu Asn Thr Asn Leu His Ser Asp Val Asp
865                 870                 875                 880

Asn Ile Asp Phe Lys Ser Leu Leu Gly Cys Leu Gly Ser Gln Cys Gly
                885                 890                 895

Ser Ser Ser Arg Ser Leu Leu Glu Asp Leu Leu Phe Asn Lys Val Lys
            900                 905                 910

Leu Ser Asp Val Gly Phe Val Glu Ala Tyr Asn Asn Cys Thr Gly Gly
        915                 920                 925

Ser Glu Ile Arg Asp Leu Leu Cys Val Gln Ser Phe Asn Gly Ile Lys
    930                 935                 940

Val Leu Pro Pro Ile Leu Ser Glu Thr Gln Ile Ser Gly Tyr Thr Thr
945                 950                 955                 960

Ala Ala Thr Val Ala Ala Met Phe Pro Pro Trp Ser Ala Ala Ala Gly
                965                 970                 975

Val Pro Phe Ser Leu Asn Val Gln Tyr Arg Ile Asn Gly Leu Gly Val
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           980                 985                 990

Thr Met Asp Val Leu Asn Lys Asn  Gln Lys Leu Ile Ala  Asn Ala Phe
        995                1000                1005

Asn Lys  Ala Leu Leu Ser Ile  Gln Asn Gly Phe Thr  Ala Thr Asn
    1010                1015                1020

Ser Ala  Leu Ala Lys Ile Gln  Ser Val Val Asn Ala  Asn Ala Gln
    1025                1030                1035

Ala Leu  Asn Ser Leu Leu Gln  Gln Leu Phe Asn Lys  Phe Gly Ala
    1040                1045                1050

Ile Ser  Ser Ser Leu Gln Glu  Ile Leu Ser Arg Leu  Asp Asn Leu
    1055                1060                1065

Glu Ala  Gln Val Gln Ile Asp  Arg Leu Ile Asn Gly  Arg Leu Thr
    1070                1075                1080

Ala Leu  Asn Ala Tyr Val Ser  Gln Gln Leu Ser Asp  Ile Thr Leu
    1085                1090                1095

Ile Lys  Ala Gly Ala Ser Arg  Ala Ile Glu Lys Val  Asn Glu Cys
    1100                1105                1110

Val Lys  Ser Gln Ser Pro Arg  Ile Asn Phe Cys Gly  Asn Gly Asn
    1115                1120                1125

His Ile  Leu Ser Leu Val Gln  Asn Ala Pro Tyr Gly  Leu Leu Phe
    1130                1135                1140

Ile His  Phe Ser Tyr Lys Pro  Thr Ser Phe Lys Thr  Val Leu Val
    1145                1150                1155

Ser Pro  Gly Leu Cys Leu Ser  Gly Asp Arg Gly Ile  Ala Pro Lys
    1160                1165                1170

Gln Gly  Tyr Phe Ile Lys Gln  Asn Asp Ser Trp Met  Phe Thr Gly
    1175                1180                1185

Ser Ser  Tyr Tyr Tyr Pro Glu  Pro Ile Ser Asp Lys  Asn Val Val
    1190                1195                1200

Phe Met  Asn Ser Cys Ser Val  Asn Phe Thr Lys Ala  Pro Phe Ile
    1205                1210                1215

Tyr Leu  Asn Asn Ser Ile Pro  Asn Leu Ser Asp Phe  Glu Ala Glu
    1220                1225                1230

Leu Ser  Leu Trp Phe Lys Asn  His Thr Ser Ile Ala  Pro Asn Leu
    1235                1240                1245

Thr Phe  Asn Ser His Ile Asn  Ala Thr Phe Leu Asp  Leu Tyr Tyr
    1250                1255                1260

Glu Met  Asn Val Ile Gln Glu  Ser Ile Lys Ser Leu  Asn Ser Ser
    1265                1270                1275

Phe Ile  Asn Leu Lys Glu Ile  Gly Thr Tyr Glu Met  Tyr Val Lys
    1280                1285                1290

Trp Pro  Trp Tyr Ile Trp Leu  Leu Ile Val Ile Leu  Phe Ile Ile
    1295                1300                1305

Phe Leu  Met Ile Leu Phe Phe  Ile Cys Cys Cys Thr  Gly Cys Gly
    1310                1315                1320

Ser Ala  Cys Phe Ser Lys Cys  His Asn Cys Cys Asp  Glu Tyr Gly
    1325                1330                1335

Gly His  Asn Asp Phe Val Ile  Lys Ala Ser His Asp  Asp
    1340                1345                1350


<210> SEQ ID NO 32
<211> LENGTH: 526
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 32

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Met Phe Ile Phe Leu Leu Phe Leu Thr Leu Thr Ser Gly Ser Asp Leu
1               5                  10                  15

Asp Arg Ala Leu Ser Gly Ile Ala Ala Glu Gln Asp Arg Asn Thr Arg
            20                  25                  30

Glu Val Phe Ala Gln Val Lys Gln Met Tyr Lys Thr Pro Thr Leu Lys
        35                  40                  45

Tyr Phe Gly Gly Phe Asn Phe Ser Gln Ile Leu Pro Asp Pro Leu Lys
    50                  55                  60

Pro Thr Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr
65                  70                  75                  80

Leu Ala Asp Ala Gly Phe Met Lys Gln Tyr Gly Glu Cys Leu Gly Asp
                85                  90                  95

Ile Asn Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr
            100                 105                 110

Val Leu Pro Pro Leu Leu Thr Asp Asp Met Ile Ala Ala Tyr Thr Ala
        115                 120                 125

Ala Leu Val Ser Gly Thr Ala Thr Ala Gly Trp Thr Phe Gly Ala Gly
    130                 135                 140

Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn
145                 150                 155                 160

Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn Gln Lys Gln Ile
                165                 170                 175

Ala Asn Gln Phe Asn Lys Ala Ile Ser Gln Ile Gln Glu Ser Leu Thr
            180                 185                 190

Thr Thr Ser Thr Ala Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn
        195                 200                 205

Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly
    210                 215                 220

Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg Leu Asp Lys Val
225                 230                 235                 240

Glu Ala Glu Val Gln Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser
                245                 250                 255

Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg
            260                 265                 270

Ala Ser Ala Asn Leu Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly
        275                 280                 285

Gln Ser Lys Arg Val Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser
    290                 295                 300

Phe Pro Gln Ala Ala Pro His Gly Val Val Phe Leu His Val Thr Tyr
305                 310                 315                 320

Val Pro Ser Gln Glu Arg Asn Phe Thr Thr Ala Pro Ala Ile Cys His
                325                 330                 335

Glu Gly Lys Ala Tyr Phe Pro Arg Glu Gly Val Phe Val Phe Asn Gly
            340                 345                 350

Thr Ser Trp Phe Ile Thr Gln Arg Asn Phe Phe Ser Pro Gln Ile Ile
        355                 360                 365

Thr Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly
    370                 375                 380

Ile Ile Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser
385                 390                 395                 400
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Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp
                405                 410                 415

Val Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile
            420                 425                 430

Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu
        435                 440                 445

Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys
    450                 455                 460

Trp Pro Trp Tyr Val Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile
465                 470                 475                 480

Val Met Val Thr Ile Leu Leu Cys Cys Met Thr Ser Cys Cys Ser Cys
                485                 490                 495

Leu Lys Gly Ala Cys Ser Cys Gly Ser Cys Cys Lys Phe Asp Glu Asp
            500                 505                 510

Asp Ser Glu Pro Val Leu Lys Gly Val Lys Leu His Tyr Thr
        515                 520                 525


<210> SEQ ID NO 33
<211> LENGTH: 588
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 33

Met Ile His Ser Val Phe Leu Leu Met Phe Leu Leu Thr Pro Thr Glu
1               5                   10                  15

Ser Asp Cys Lys Leu Pro Leu Gly Gln Ser Leu Cys Ala Leu Pro Asp
            20                  25                  30

Thr Pro Ser Thr Leu Thr Pro Arg Ser Val Arg Ser Val Pro Gly Glu
        35                  40                  45

Met Arg Leu Ala Ser Ile Ala Phe Asn His Pro Ile Gln Val Asp Gln
    50                  55                  60

Leu Asn Ser Ser Tyr Phe Lys Leu Ser Ile Pro Thr Asn Phe Ser Phe
65                  70                  75                  80

Gly Val Thr Gln Glu Tyr Ile Gln Thr Thr Ile Gln Lys Val Thr Val
                85                  90                  95

Asp Cys Lys Gln Tyr Val Cys Asn Gly Phe Gln Lys Cys Glu Gln Leu
            100                 105                 110

Leu Arg Glu Tyr Gly Gln Phe Cys Ser Lys Ile Asn Gln Ala Leu His
        115                 120                 125

Gly Ala Asn Leu Arg Gln Asp Asp Ser Val Arg Asn Leu Phe Ala Ser
    130                 135                 140

Val Lys Ser Ser Gln Ser Ser Pro Ile Ile Pro Gly Phe Gly Gly Asp
145                 150                 155                 160

Phe Asn Leu Thr Leu Leu Glu Pro Val Ser Ile Ser Thr Gly Ser Arg
                165                 170                 175

Ser Ala Arg Ser Ala Ile Glu Asp Leu Leu Phe Asp Lys Val Thr Ile
            180                 185                 190

Ala Asp Pro Gly Tyr Met Gln Gly Tyr Asp Asp Cys Met Gln Gln Gly
        195                 200                 205

Pro Ala Ser Ala Arg Asp Leu Ile Cys Ala Gln Tyr Val Ala Gly Tyr
    210                 215                 220

Lys Val Leu Pro Pro Leu Met Asp Val Asn Met Glu Ala Ala Tyr Thr
225                 230                 235                 240
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Ser Ser Leu Leu Gly Ser Ile Ala Gly Val Gly Trp Thr Ala Gly Leu
                245                 250                 255

Ser Ser Phe Ala Ala Ile Pro Phe Ala Gln Ser Ile Phe Tyr Arg Leu
            260                 265                 270

Asn Gly Val Gly Ile Thr Gln Gln Val Leu Ser Glu Asn Gln Lys Leu
        275                 280                 285

Ile Ala Asn Lys Phe Asn Gln Ala Leu Gly Ala Met Gln Thr Gly Phe
    290                 295                 300

Thr Thr Thr Asn Glu Ala Phe Gln Lys Val Gln Asp Ala Val Asn Asn
305                 310                 315                 320

Asn Ala Gln Ala Leu Ser Lys Leu Ala Ser Glu Leu Ser Asn Thr Phe
                325                 330                 335

Gly Ala Ile Ser Ala Ser Ile Gly Asp Ile Ile Gln Arg Leu Asp Val
            340                 345                 350

Leu Glu Gln Asp Ala Gln Ile Asp Arg Leu Ile Asn Gly Arg Leu Thr
        355                 360                 365

Thr Leu Asn Ala Phe Val Ala Gln Gln Leu Val Arg Ser Glu Ser Ala
    370                 375                 380

Ala Leu Ser Ala Gln Leu Ala Lys Asp Lys Val Asn Glu Cys Val Lys
385                 390                 395                 400

Ala Gln Ser Lys Arg Ser Gly Phe Cys Gly Gln Gly Thr His Ile Val
                405                 410                 415

Ser Phe Val Val Asn Ala Pro Asn Gly Leu Tyr Phe Met His Val Gly
            420                 425                 430

Tyr Tyr Pro Ser Asn His Ile Glu Val Val Ser Ala Tyr Gly Leu Cys
        435                 440                 445

Asp Ala Ala Asn Pro Thr Asn Cys Ile Ala Pro Val Asn Gly Tyr Phe
    450                 455                 460

Ile Lys Thr Asn Asn Thr Arg Ile Val Asp Glu Trp Ser Tyr Thr Gly
465                 470                 475                 480

Ser Ser Phe Tyr Ala Pro Glu Pro Ile Thr Ser Leu Asn Thr Lys Tyr
                485                 490                 495

Val Ala Pro Gln Val Thr Tyr Gln Asn Ile Ser Thr Asn Leu Pro Pro
            500                 505                 510

Pro Leu Leu Gly Asn Ser Thr Gly Ile Asp Phe Gln Asp Glu Leu Asp
        515                 520                 525

Glu Phe Phe Lys Asn Val Ser Thr Ser Ile Pro Asn Phe Gly Ser Leu
    530                 535                 540

Thr Gln Ile Asn Thr Thr Leu Leu Asp Leu Thr Tyr Glu Met Leu Ser
545                 550                 555                 560

Leu Gln Gln Val Val Lys Ala Leu Asn Glu Ser Tyr Ile Asp Leu Lys
                565                 570                 575

Glu Leu Gly Asn Tyr Thr Tyr Tyr Asn Lys Trp Pro
            580                 585


<210> SEQ ID NO 34
<211> LENGTH: 526
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 34

Met Phe Ile Phe Leu Leu Phe Leu Thr Leu Thr Ser Gly Ser Asp Leu
1               5                   10                  15
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Asp Arg Ala Leu Ser Gly Ile Ala Ala Glu Gln Asp Arg Asn Thr Arg
            20                  25                  30

Glu Val Phe Ala Gln Val Lys Gln Met Tyr Lys Thr Pro Thr Leu Lys
        35                  40                  45

Tyr Phe Gly Gly Phe Asn Phe Ser Gln Ile Leu Pro Asp Pro Leu Lys
    50                  55                  60

Pro Thr Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr
65                  70                  75                  80

Leu Ala Asp Ala Gly Phe Met Lys Gln Tyr Gly Glu Cys Leu Gly Asp
                85                  90                  95

Ile Asn Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr
            100                 105                 110

Val Leu Pro Pro Leu Leu Thr Asp Asp Met Ile Ala Ala Tyr Thr Ala
        115                 120                 125

Ala Leu Val Ser Gly Thr Ala Thr Ala Gly Trp Thr Phe Gly Ala Gly
    130                 135                 140

Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn
145                 150                 155                 160

Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn Gln Lys Gln Ile
                165                 170                 175

Ala Asn Gln Phe Asn Lys Ala Ile Ser Gln Ile Gln Glu Ser Leu Thr
            180                 185                 190

Thr Thr Ser Thr Ala Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn
        195                 200                 205

Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly
    210                 215                 220

Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg Leu Asp Lys Val
225                 230                 235                 240

Glu Ala Glu Val Gln Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser
                245                 250                 255

Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg
            260                 265                 270

Ala Ser Ala Asn Leu Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly
        275                 280                 285

Gln Ser Lys Arg Val Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser
    290                 295                 300

Phe Pro Gln Ala Ala Pro His Gly Val Val Phe Leu His Val Thr Tyr
305                 310                 315                 320

Val Pro Ser Gln Glu Arg Asn Phe Thr Thr Ala Pro Ala Ile Cys His
                325                 330                 335

Glu Gly Lys Ala Tyr Phe Pro Arg Glu Gly Val Phe Val Phe Asn Gly
            340                 345                 350

Thr Ser Trp Phe Ile Thr Gln Arg Asn Phe Phe Ser Pro Gln Ile Ile
        355                 360                 365

Thr Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly
    370                 375                 380

Ile Ile Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser
385                 390                 395                 400

Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp
                405                 410                 415

Val Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile
            420                 425                 430
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Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu
        435                 440                 445

Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys
    450                 455                 460

Trp Pro Trp Tyr Val Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile
465                 470                 475                 480

Val Met Val Thr Ile Leu Leu Cys Cys Met Thr Ser Cys Cys Ser Cys
                485                 490                 495

Leu Lys Gly Ala Cys Ser Cys Gly Ser Cys Cys Lys Phe Asp Glu Asp
            500                 505                 510

Asp Ser Glu Pro Val Leu Lys Gly Val Lys Leu His Tyr Thr
        515                 520                 525


<210> SEQ ID NO 35
<211> LENGTH: 1864
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 35

tcaagctttt ggaccctcgt acagaagcta atacgactca ctatagggaa ataagagaga     60

aaagaagagt aagaagaaat ataagagcca ccatgggtct caaggtgaac gtctctgccg    120

tattcatggc agtactgtta actctccaaa cacccgccgg tcaaattcat tggggcaatc    180

tctctaagat aggggtagta ggaataggaa gtgcaagcta caaagttatg actcgttcca    240

gccatcaatc attagtcata aaattaatgc ccaatataac tctcctcaat aactgcacga    300

gggtagagat tgcagaatac aggagactac taagaacagt tttggaacca attagggatg    360

cacttaatgc aatgacccag aacataaggc cggttcagag cgtagcttca agtaggagac    420

acaagagatt tgcgggagta gtcctggcag gtgcggccct aggtgttgcc acagctgctc    480

agataacagc cggcattgca cttcaccggt ccatgctgaa ctctcaggcc atcgacaatc    540

tgagagcgag cctggaaact actaatcagg caattgaggc aatcagacaa gcagggcagg    600

agatgatatt ggctgttcag ggtgtccaag actacatcaa taatgagctg ataccgtcta    660

tgaaccagct atcttgtgat ctaatcggtc agaagctcgg gctcaaattg cttagatact    720

atacagaaat cctgtcatta tttggcccca gcctacggga ccccatatct gcggagatat    780

ctatccaggc tttgagttat gcacttggag gagatatcaa taaggtgtta gaaaagctcg    840

gatacagtgg aggcgattta ctaggcatct tagagagcag aggaataaag gctcggataa    900

ctcacgtcga cacagagtcc tacttcatag tcctcagtat agcctatccg acgctgtccg    960

agattaaggg ggtgattgtc caccggctag agggggtctc gtacaacata ggctctcaag   1020

agtggtatac cactgtgccc aagtatgttg caacccaagg gtaccttatc tcgaattttg   1080

atgagtcatc atgtactttc atgccagagg ggactgtgtg cagccaaaat gccttgtacc   1140

cgatgagtcc tctgctccaa gaatgcctcc gggggtccac caagtcctgt gctcgtacac   1200

tcgtatccgg gtcttttggg aaccggttca ttttatcaca agggaaccta atagccaatt   1260

gtgcatcaat tctttgtaag tgttacacaa caggtacgat tattaatcaa gaccctgaca   1320

agatcctaac atacattgct gccgatcgct gcccggtagt cgaggtgaac ggcgtgacca   1380

tccaagtcgg gagcaggagg tatccagacg ctgtgtactt gcacagaatt gacctcggtc   1440

ctcccatatc attggagagg ttggacgtag ggacaaatct ggggaatgca attgccaaat   1500

tggaggatgc caaggaattg ttggaatcat cggaccagat attgagaagt atgaaaggtt   1560
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tatcgagcac tagcatagtc tacatcctga ttgcagtgtg tcttggaggg ttgataggga 1620

tccccacttt aatatgttgc tgcaggggggc gttgtaacaa aaagggagaa caagttggta 1680

tgtcaagacc aggcctaaag cctgacctta caggaacatc aaaatcctat gtaagatcgc 1740

tttgatgata ataggctgga gcctcggtgg ccaagcttct tgccccttgg gcctcccccc 1800

agcccctcct ccccttcctg cacccgtacc cccgtggtct ttgaataaag tctgagtggg 1860

cggc 1864

<210> SEQ ID NO 36
<211> LENGTH: 1653
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 36

atgggtctca aggtgaacgt ctctgccgta ttcatggcag tactgttaac tctccaaaca 60

cccgccggtc aaattcattg gggcaatctc tctaagatag gggtagtagg aataggaagt 120

gcaagctaca aagttatgac tcgttccagc catcaatcat tagtcataaa attaatgccc 180

aatataactc tcctcaataa ctgcacgagg gtagagattg cagaatacag gagactacta 240

agaacagttt tggaaccaat tagggatgca cttaatgcaa tgacccagaa cataaggccg 300

gttcagagcg tagcttcaag taggagacac aagagatttg cgggagtagt cctggcaggt 360

gcggccctag gtgttgccac agctgctcag ataacagccg gcattgcact tcaccggtcc 420

atgctgaact ctcaggccat cgacaatctg agagcgagcc tggaaactac taatcaggca 480

attgaggcaa tcagacaagc agggcaggag atgatattgg ctgttcaggg tgtccaagac 540

tacatcaata atgagctgat accgtctatg aaccagctat cttgtgatct aatcggtcag 600

aagctcgggc tcaaattgct tagatactat acagaaatcc tgtcattatt tggccccagc 660

ctacgggacc ccatatctgc ggagatatct atccaggctt tgagttatgc acttggagga 720

gatatcaata aggtgttaga aaagctcgga tacagtggag gcgatttact aggcatctta 780

gagagcagag gaataaaggc tcggataact cacgtcgaca cagagtccta cttcatagtc 840

ctcagtatag cctatccgac gctgtccgag attaaggggg tgattgtcca ccggctagag 900

ggggtctcgt acaacatagg ctctcaagag tggtatacca ctgtgcccaa gtatgttgca 960

acccaagggt accttatctc gaattttgat gagtcatcat gtactttcat gccagagggg 1020

actgtgtgca gccaaaatgc cttgtacccg atgagtcctc tgctccaaga atgcctccgg 1080

gggtccacca agtcctgtgc tcgtacactc gtatccgggt cttttgggaa ccggttcatt 1140

ttatcacaag ggaacctaat agccaattgt gcatcaattc tttgtaagtg ttacacaaca 1200

ggtacgatta ttaatcaaga ccctgacaag atcctaacat acattgctgc cgatcgctgc 1260

ccggtagtcg aggtgaacgg cgtgaccatc caagtcggga gcaggaggta tccagacgct 1320

gtgtacttgc acagaattga cctcggtcct cccatatcat tggagaggtt ggacgtaggg 1380

acaaatctgg ggaatgcaat tgccaaattg gaggatgcca aggaattgtt ggaatcatcg 1440

gaccagatat tgagaagtat gaaaggttta tcgagcacta gcatagtcta catcctgatt 1500

gcagtgtgtc ttggagggtt gatagggatc cccactttaa tatgttgctg caggggggcgt 1560

tgtaacaaaa agggagaaca agttggtatg tcaagaccag gcctaaagcc tgaccttaca 1620

ggaacatcaa aatcctatgt aagatcgctt tga 1653

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<210> SEQ ID NO 37
<211> LENGTH: 1925
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 37

ggggaaataa gagagaaaag aagagtaaga agaaatataa gagccaccat gggtctcaag 60

gtgaacgtct ctgccgtatt catggcagta ctgttaactc tccaaacacc cgccggtcaa 120

attcattggg gcaatctctc taagataggg gtagtaggaa taggaagtgc aagctacaaa 180

gttatgactc gttccagcca tcaatcatta gtcataaaat taatgcccaa tataactctc 240

ctcaataact gcacgagggt agagattgca gaatacagga gactactaag aacagttttg 300

gaaccaatta gggatgcact taatgcaatg acccagaaca taaggccggt tcagagcgta 360

gcttcaagta ggagacacaa gagatttgcg ggagtagtcc tggcaggtgc ggccctaggt 420

gttgccacag ctgctcagat aacagccggc attgcacttc accggtccat gctgaactct 480

caggccatcg acaatctgag agcgagcctg gaaactacta atcaggcaat tgaggcaatc 540

agacaagcag ggcaggagat gatattggct gttcagggtg tccaagacta catcaataat 600

gagctgatac cgtctatgaa ccagctatct tgtgatctaa tcggtcagaa gctcgggctc 660

aaattgctta gatactatac agaaatcctg tcattatttg gccccagcct acgggacccc 720

atatctgcgg agatatctat ccaggctttg agttatgcac ttggaggaga tatcaataag 780

gtgttagaaa agctcggata cagtggaggc gatttactag gcatcttaga gagcagagga 840

ataaaggctc ggataactca cgtcgacaca gagtcctact tcatagtcct cagtatagcc 900

tatccgacgc tgtccgagat taaggggtg attgtccacc ggctagaggg ggtctcgtac 960

aacataggct ctcaagagtg gtataccact gtgcccaagt atgttgcaac ccaagggtac 1020

cttatctcga attttgatga gtcatcatgt actttcatgc cagaggggac tgtgtgcagc 1080

caaaatgcct tgtacccgat gagtcctctg ctccaagaat gcctccgggg gtccaccaag 1140

tcctgtgctc gtacactcgt atccgggtct tttgggaacc ggttcatttt atcacaaggg 1200

aacctaatag ccaattgtgc atcaattctt tgtaagtgtt acacaacagg tacgattatt 1260

aatcaagacc ctgacaagat cctaacatac attgctgccg atcgctgccc ggtagtcgag 1320

gtgaacggcg tgaccatcca agtcgggagc aggaggtatc cagacgctgt gtacttgcac 1380

agaattgacc tcggtcctcc catatcattg gagaggttgg acgtagggac aaatctgggg 1440

aatgcaattg ccaaattgga ggatgccaag gaattgttgg aatcatcgga ccagatattg 1500

agaagtatga aaggtttatc gagcactagc atagtctaca tcctgattgc agtgtgtctt 1560

ggagggttga tagggatccc cactttaata tgttgctgca gggggcgttg taacaaaaag 1620

ggagaacaag ttggtatgtc aagaccaggc ctaaagcctg accttacagg aacatcaaaa 1680

tcctatgtaa gatcgctttg atgataatag gctggagcct cggtggccaa gcttcttgcc 1740

ccttgggcct ccccccagcc cctcctcccc ttcctgcacc cgtacccccg tggtctttga 1800

ataaagtctg agtgggcggc aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1860

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1920

tctag 1925

<210> SEQ ID NO 38
<211> LENGTH: 1864

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 38

tcaagctttt ggaccctcgt acagaagcta atacgactca ctatagggaa ataagagaga 60

aaagaagagt aagaagaaat ataagagcca ccatgggtct caaggtgaac gtctctgtca 120

tattcatggc agtactgtta actcttcaaa cacccaccgg tcaaatccat tggggcaatc 180

tctctaagat aggggtggta ggggtaggaa gtgcaagcta caaagttatg actcgttcca 240

gccatcaatc attagtcata aagttaatgc ccaatataac tctcctcaac aattgcacga 300

gggtagggat tgcagaatac aggagactac tgagaacagt tctggaacca attagagatg 360

cacttaatgc aatgacccag aatataagac cggttcagag tgtagcttca agtaggagac 420

acaagagatt tgcgggagtt gtcctggcag gtgcggccct aggcgttgcc acagctgctc 480

aaataacagc cggtattgca cttcaccagt ccatgctgaa ctctcaagcc atcgacaatc 540

tgagagcgag cctagaaact actaatcagg caattgaggc aatcagacaa gcagggcagg 600

agatgatatt ggctgttcag ggtgtccaag actacatcaa taatgagctg ataccgtcta 660

tgaatcaact atcttgtgat ttaatcggcc agaagctagg gctcaaattg ctcagatact 720

atacagaaat cctgtcatta tttggcccca gcttacggga ccccatatct gcggagatat 780

ctatccaggc tttgagctat gcgcttggag gagatatcaa taaggtgttg gaaaagctcg 840

gatacagtgg aggtgatcta ctgggcatct tagagagcag aggaataaag gcccggataa 900

ctcacgtcga cacagagtcc tacttcattg tactcagtat agcctatccg acgctatccg 960

agattaaggg ggtgattgtc caccggctag agggggtctc gtacaacata ggctctcaag 1020

agtggtatac cactgtgccc aagtatgttg caacccaagg gtaccttatc tcgaattttg 1080

atgagtcatc atgcactttc atgccagagg ggactgtgtg cagccagaat gccttgtacc 1140

cgatgagtcc tctgctccaa gaatgcctcc gggggtccac taagtcctgt gctcgtacac 1200

tcgtatccgg gtctttcggg aaccggttca ttttatcaca ggggaaccta atagccaatt 1260

gtgcatcaat cctttgcaag tgttacacaa caggaacaat cattaatcaa gaccctgaca 1320

agatcctaac atacattgct gccgatcact gcccggtggt cgaggtgaat ggcgtgacca 1380

tccaagtcgg gagcaggagg tatccggacg ctgtgtactt gcacaggatt gacctcggtc 1440

ctcccatatc tttggagagg ttggacgtag ggacaaatct ggggaatgca attgctaagt 1500

tggaggatgc caaggaattg ttggagtcat cggaccagat attgaggagt atgaaaggtt 1560

tatcgagcac tagtatagtt tacatcctga ttgcagtgtg tcttggagga ttgataggga 1620

tccccgcttt aatatgttgc tgcaggggggc gttgtaacaa gaagggagaa caagttggta 1680

tgtcaagacc aggcctaaag cctgatctta caggaacatc aaaatcctat gtaaggtcac 1740

tctgatgata ataggctgga gcctcggtgg ccaagcttct tgccccttgg gcctcccccc 1800

agcccctcct ccccttcctg cacccgtacc cccgtggtct ttgaataaag tctgagtggg 1860

cggc 1864

<210> SEQ ID NO 39
<211> LENGTH: 1653
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

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<400> SEQUENCE: 39

atgggtctca aggtgaacgt ctctgtcata ttcatggcag tactgttaac tcttcaaaca 60

cccaccggtc aaatccattg gggcaatctc tctaagatag gggtggtagg ggtaggaagt 120

gcaagctaca aagttatgac tcgttccagc catcaatcat tagtcataaa gttaatgccc 180

aatataactc tcctcaacaa ttgcacgagg gtagggattg cagaatacag gagactactg 240

agaacagttc tggaaccaat tagagatgca cttaatgcaa tgacccagaa tataagaccg 300

gttcagagtg tagcttcaag taggagacac aagagatttg cgggagttgt cctggcaggt 360

gcggccctag gcgttgccac agctgctcaa ataacagccg gtattgcact tcaccagtcc 420

atgctgaact ctcaagccat cgacaatctg agagcgagcc tagaaactac taatcaggca 480

attgaggcaa tcagacaagc agggcaggag atgatattgg ctgttcaggg tgtccaagac 540

tacatcaata atgagctgat accgtctatg aatcaactat cttgtgattt aatcggccag 600

aagctagggc tcaaattgct cagatactat acagaaatcc tgtcattatt tggccccagc 660

ttacgggacc ccatatctgc ggagatatct atccaggctt tgagctatgc gcttggagga 720

gatatcaata aggtgttgga aaagctcgga tacagtggag gtgatctact gggcatctta 780

gagagcagag gaataaaggc ccggataact cacgtcgaca cagagtccta cttcattgta 840

ctcagtatag cctatccgac gctatccgag attaaggggg tgattgtcca ccggctagag 900

ggggtctcgt acaacatagg ctctcaagag tggtatacca ctgtgcccaa gtatgttgca 960

acccaagggt accttatctc gaattttgat gagtcatcat gcactttcat gccagagggg 1020

actgtgtgca gccagaatgc cttgtacccg atgagtcctc tgctccaaga atgcctccgg 1080

gggtccacta agtcctgtgc tcgtacactc gtatccgggt ctttcgggaa ccggttcatt 1140

ttatcacagg ggaacctaat agccaattgt gcatcaatcc tttgcaagtg ttacacaaca 1200

ggaacaatca ttaatcaaga ccctgacaag atcctaacat acattgctgc cgatcactgc 1260

ccggtggtcg aggtgaatgg cgtgaccatc caagtcggga gcaggaggta tccggacgct 1320

gtgtacttgc acaggattga cctcggtcct cccatatctt tggagaggtt ggacgtaggg 1380

acaaatctgg ggaatgcaat tgctaagttg gaggatgcca aggaattgtt ggagtcatcg 1440

gaccagatat tgaggagtat gaaaggttta tcgagcacta gtatagttta catcctgatt 1500

gcagtgtgtc ttggaggatt gatagggatc cccgctttaa tatgttgctg cagggggcgt 1560

tgtaacaaga agggagaaca agttggtatg tcaagaccag gcctaaagcc tgatcttaca 1620

ggaacatcaa aatcctatgt aaggtcactc tga 1653

<210> SEQ ID NO 40
<211> LENGTH: 1925
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 40

ggggaaataa gagagaaaag aagagtaaga agaaatataa gagccaccat gggtctcaag 60

gtgaacgtct ctgtcatatt catggcagta ctgttaactc ttcaaacacc caccggtcaa 120

atccattggg gcaatctctc taagataggg gtggtagggg taggaagtgc aagctacaaa 180

gttatgactc gttccagcca tcaatcatta gtcataaagt taatgcccaa tataactctc 240

ctcaacaatt gcacgagggt agggattgca gaatacagga gactactgag aacagttctg 300

gaaccaatta gagatgcact taatgcaatg acccagaata taagaccggt tcagagtgta 360

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gcttcaagta ggagacacaa gagatttgcg ggagttgtcc tggcaggtgc ggccctaggc 420

gttgccacag ctgctcaaat aacagccggt attgcacttc accagtccat gctgaactct 480

caagccatcg acaatctgag agcgagccta gaaactacta atcaggcaat tgaggcaatc 540

agacaagcag ggcaggagat gatattggct gttcagggtg tccaagacta catcaataat 600

gagctgatac cgtctatgaa tcaactatct tgtgatttaa tcggccagaa gctagggctc 660

aaattgctca gatactatac agaaatcctg tcattatttg gccccagctt acgggacccc 720

atatctgcgg agatatctat ccaggctttg agctatgcgc ttggaggaga tatcaataag 780

gtgttggaaa agctcggata cagtggaggt gatctactgg gcatcttaga gagcagagga 840

ataaaggccc ggataactca cgtcgacaca gagtcctact tcattgtact cagtatagcc 900

tatccgacgc tatccgagat taaggggtg attgtccacc ggctagaggg ggtctcgtac 960

aacataggct ctcaagagtg gtataccact gtgcccaagt atgttgcaac ccaagggtac 1020

cttatctcga attttgatga gtcatcatgc actttcatgc cagaggggac tgtgtgcagc 1080

cagaatgcct tgtacccgat gagtcctctg ctccaagaat gcctccgggg gtccactaag 1140

tcctgtgctc gtacactcgt atccgggtct ttcgggaacc ggttcatttt atcacagggg 1200

aacctaatag ccaattgtgc atcaatcctt tgcaagtgtt acacaacagg aacaatcatt 1260

aatcaagacc ctgacaagat cctaacatac attgctgccg atcactgccc ggtggtcgag 1320

gtgaatggcg tgaccatcca agtcgggagc aggaggtatc cggacgctgt gtacttgcac 1380

aggattgacc tcggtcctcc catatctttg gagaggttgg acgtagggac aaatctgggg 1440

aatgcaattg ctaagttgga ggatgccaag gaattgttgg agtcatcgga ccagatattg 1500

aggagtatga aaggtttatc gagcactagt atagtttaca tcctgattgc agtgtgtctt 1560

ggaggattga tagggatccc cgctttaata tgttgctgca gggggcgttg taacaagaag 1620

ggagaacaag ttggtatgtc aagaccaggc ctaaagcctg atcttacagg aacatcaaaa 1680

tcctatgtaa ggtcactctg atgataatag gctggagcct cggtggccaa gcttcttgcc 1740

ccttgggcct ccccccagcc cctcctcccc ttcctgcacc cgtacccccg tggtctttga 1800

ataaagtctg agtgggcggc aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1860

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1920

tctag 1925

<210> SEQ ID NO 41
<211> LENGTH: 2065
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 41

tcaagctttt ggaccctcgt acagaagcta atacgactca ctatagggaa ataagagaga 60

aaagaagagt aagaagaaat ataagagcca ccatgtcacc gcaacgagac cggataaatg 120

ccttctacaa agataaccct tatcccaagg gaagtaggat agttattaac agagaacatc 180

ttatgattga cagaccctat gttctgctgg ctgttctgtt cgtcatgttt ctgagcttga 240

tcggattgct ggcaattgca ggcattagac ttcatcgggc agccatctac accgcggaga 300

tccataaaag cctcagtacc aatctggatg tgactaactc catcgagcat caggtcaagg 360

acgtgctgac accactcttt aaaatcatcg gggatgaagt gggcctgaga acacctcaga 420

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gattcactga cctagtgaaa ttcatctcgg acaagattaa attccttaat ccggataggg 480

agtacgactt cagagatctc acttggtgca tcaacccgcc agagaggatc aaactagatt 540

atgatcaata ctgtgcagat gtggctgctg aagagctcat gaatgcattg gtgaactcaa 600

ctctactgga gaccagaaca accactcagt tcctagctgt ctcaaaggga aactgctcag 660

ggcccactac aatcagaggt caattctcaa acatgtcgct gtccttgttg gacttgtact 720

taggtcgagg ttacaatgtg tcatctatag tcactatgac atcccaggga atgtatgggg 780

gaacctacct agttgaaaag cctaatctga acagcaaagg gtcagagttg tcacaactga 840

gcatgtaccg agtgtttgaa gtaggtgtga tcagaaaccc gggtttgggg gctccggtgt 900

tccatatgac aaactatttt gagcaaccag tcagtaatgg tctcggcaac tgtatggtgg 960

ctttgggggga gctcaaactc gcagcccttt gtcacgggga cgattctatc ataattccct 1020

atcagggatc agggaaaggt gtcagcttcc agctcgtcaa gctgggtgtc tggaaatccc 1080

caaccgacat gcaatcctgg gtccccttat caacggatga tccagtggta gacaggcttt 1140

acctctcatc tcacagaggt gtcatcgctg acaatcaagc aaaatgggct gtcccgacaa 1200

cacgaacaga tgacaagttg cgaatggaga catgcttcca gcaggcgtgt aaaggtaaaa 1260

tccaagcact ctgcgagaat cccgagtggg taccattgaa ggataacagg attccttcat 1320

acggggtcct gtctgttgat ctgagtctga cggttgagct taaaatcaaa attgcttcgg 1380

gattcgggcc attgatcaca cacggctcag ggatggacct atacaaatcc aactgcaaca 1440

atgtgtattg gctgactatt ccgccaatga gaaatctagc cttaggcgta atcaacacat 1500

tggagtggat accgagattc aaggttagtc ccaacctctt cactgtccca attaaggaag 1560

caggcgaaga ctgccatgcc ccaacatacc tacctgcgga ggtggacggt gatgtcaaac 1620

tcagttccaa cctggtgatt ctacctggtc aagatctcca atatgttttg gcaacctacg 1680

atacctccag ggttgagcat gctgtggttt attacgttta cagcccaagc cgctcatttt 1740

cttacttttа tccttttagg ttgcctataa agggggtccc aatcgaacta caagtggaat 1800

gcttcacatg ggatcaaaaa ctctggtgcc gtcacttctg tgtgcttgcg gactcagaat 1860

ccggtggact tatcactcac tctgggatgg tgggcatggg agtcagctgc acagctaccc 1920

gggaagatgg aaccaatcgc agataatgat aataggctgg agcctcggtg gccaagcttc 1980

ttgcccctg ggcctccccc cagcccctcc tccccttcct gcacccgtac ccccgtggtc 2040

tttgaataaa gtctgagtgg gcggc 2065

<210> SEQ ID NO 42
<211> LENGTH: 1854
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 42

atgtcaccgc aacgagaccg gataaatgcc ttctacaaag ataaccctta tcccaaggga 60

agtaggatag ttattaacag agaacatctt atgattgaca gaccctatgt tctgctggct 120

gttctgttcg tcatgtttct gagcttgatc ggattgctgg caattgcagg cattagactt 180

catcgggcag ccatctacac cgcggagatc cataaaagcc tcagtaccaa tctggatgtg 240

actaactcca tcgagcatca ggtcaaggac gtgctgacac cactctttaa aatcatcggg 300

gatgaagtgg gcctgagaac acctcagaga ttcactgacc tagtgaaatt catctcggac 360

aagattaaat tccttaatcc ggatagggag tacgacttca gagatctcac ttggtgcatc 420

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aacccgccag agaggatcaa actagattat gatcaatact gtgcagatgt ggctgctgaa 480

gagctcatga atgcattggt gaactcaact ctactggaga ccagaacaac cactcagttc 540

ctagctgtct caaagggaaa ctgctcaggg cccactacaa tcagaggtca attctcaaac 600

atgtcgctgt ccttgttgga cttgtactta ggtcgaggtt acaatgtgtc atctatagtc 660

actatgacat cccagggaat gtatggggga acctacctag ttgaaaagcc taatctgaac 720

agcaaagggt cagagttgtc acaactgagc atgtaccgag tgtttgaagt aggtgtgatc 780

agaaacccgg gtttgggggc tccggtgttc catatgacaa actattttga gcaaccagtc 840

agtaatggtc tcggcaactg tatggtggct ttgggggagc tcaaactcgc agccctttgt 900

cacggggacg attctatcat aattccctat cagggatcag ggaaaggtgt cagcttccag 960

ctcgtcaagc tgggtgtctg gaaatcccca accgacatgc aatcctgggt ccccttatca 1020

acggatgatc cagtggtaga caggctttac ctctcatctc acagaggtgt catcgctgac 1080

aatcaagcaa aatgggctgt cccgacaaca cgaacagatg acaagttgcg aatggagaca 1140

tgcttccagc aggcgtgtaa aggtaaaatc caagcactct gcgagaatcc cgagtgggta 1200

ccattgaagg ataacaggat tccttcatac ggggtcctgt ctgttgatct gagtctgacg 1260

gttgagctta aaatcaaaat tgcttcggga ttcgggccat tgatcacaca cggctcaggg 1320

atggacctat acaaatccaa ctgcaacaat gtgtattggc tgactattcc gccaatgaga 1380

aatctagcct taggcgtaat caacacattg gagtggatac cgagattcaa ggttagtccc 1440

aacctcttca ctgtcccaat taaggaagca ggcgaagact gccatgcccc aacataccta 1500

cctgcggagg tggacggtga tgtcaaactc agttccaacc tggtgattct acctggtcaa 1560

gatctccaat atgttttggc aacctacgat acctccaggg ttgagcatgc tgtggtttat 1620

tacgtttaca gcccaagccg ctcatttttct tacttttatc cttttaggtt gcctataaag 1680

ggggtcccaa tcgaactaca agtggaatgc ttcacatggg atcaaaaact ctggtgccgt 1740

cacttctgtg tgcttgcgga ctcagaatcc ggtggactta tcactcactc tgggatggtg 1800

ggcatgggag tcagctgcac agctacccgg gaagatggaa ccaatcgcag ataa 1854

<210> SEQ ID NO 43
<211> LENGTH: 2126
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 43

ggggaaataa gagagaaaag aagagtaaga agaaatataa gagccaccat gtcaccgcaa 60

cgagaccgga taaatgcctt ctacaaagat aacccttatc ccaagggaag taggatagtt 120

attaacagag aacatcttat gattgacaga ccctatgttc tgctggctgt tctgttcgtc 180

atgtttctga gcttgatcgg attgctggca attgcaggca ttagacttca tcgggcagcc 240

atctacaccg cggagatcca taaaagcctc agtaccaatc tggatgtgac taactccatc 300

gagcatcagg tcaaggacgt gctgacacca ctctttaaaa tcatcgggga tgaagtgggc 360

ctgagaacac ctcagagatt cactgaccta gtgaaattca tctcggacaa gattaaattc 420

cttaatccgg atagggagta cgacttcaga gatctcactt ggtgcatcaa cccgccagag 480

aggatcaaac tagattatga tcaatactgt gcagatgtgg ctgctgaaga gctcatgaat 540

gcattggtga actcaactct actggagacc agaacaacca ctcagttcct agctgtctca 600

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aagggaaact gctcagggcc cactacaatc agaggtcaat tctcaaacat gtcgctgtcc 660

ttgttggact tgtacttagg tcgaggttac aatgtgtcat ctatagtcac tatgacatcc 720

cagggaatgt atgggggaac ctacctagtt gaaaagccta atctgaacag caaagggtca 780

gagttgtcac aactgagcat gtaccgagtg tttgaagtag gtgtgatcag aaacccgggt 840

ttgggggctc cggtgttcca tatgacaaac tattttgagc aaccagtcag taatggtctc 900

ggcaactgta tggtggcttt gggggagctc aaactcgcag ccctttgtca cggggacgat 960

tctatcataa ttccctatca gggatcaggg aaaggtgtca gcttccagct cgtcaagctg 1020

ggtgtctgga aatccccaac cgacatgcaa tcctgggtcc ccttatcaac ggatgatcca 1080

gtggtagaca ggctttacct ctcatctcac agaggtgtca tcgctgacaa tcaagcaaaa 1140

tgggctgtcc cgacaacacg aacagatgac aagttgcgaa tggagacatg cttccagcag 1200

gcgtgtaaag gtaaaatcca agcactctgc gagaatcccg agtgggtacc attgaaggat 1260

aacaggattc cttcatacgg ggtcctgtct gttgatctga gtctgacggt tgagcttaaa 1320

atcaaaattg cttcgggatt cgggccattg atcacacacg gctcagggat ggacctatac 1380

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ggcgtaatca acacattgga gtggataccg agattcaagg ttagtcccaa cctcttcact 1500

gtcccaatta aggaagcagg cgaagactgc catgccccaa catacctacc tgcggaggtg 1560

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gttttggcaa cctacgatac ctccagggtt gagcatgctg tggtttatta cgtttacagc 1680

ccaagccgct cattttctta cttttatcct tttaggttgc ctataaaggg ggtcccaatc 1740

gaactacaag tggaatgctt cacatgggat caaaaactct ggtgccgtca cttctgtgtg 1800

cttgcggact cagaatccgg tggacttatc actcactctg ggatggtggg catgggagtc 1860

agctgcacag ctacccggga agatggaacc aatcgcagat aatgataata ggctggagcc 1920

tcggtggcca agcttcttgc cccttgggcc tccccccagc ccctcctccc cttcctgcac 1980

ccgtaccccc gtggtctttg aataaagtct gagtgggcgg caaaaaaaaa aaaaaaaaaa 2040

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2100

aaaaaaaaaa aaaaaaaaaa atctag 2126

<210> SEQ ID NO 44
<211> LENGTH: 2065
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 44

tcaagctttt ggaccctcgt acagaagcta atacgactca ctatagggaa ataagagaga 60

aaagaagagt aagaagaaat ataagagcca ccatgtcacc acaacgagac cggataaatg 120

ccttctacaa agacaacccc catcctaagg gaagtaggat agttattaac agagaacatc 180

ttatgattga tagaccttat gttttgctgg ctgttctatt cgtcatgttt ctgagcttga 240

tcgggttgct agccattgca ggcattagac ttcatcgggc agccatctac accgcagaga 300

tccataaaag cctcagcacc aatctggatg taactaactc aatcgagcat caggttaagg 360

acgtgctgac accactcttc aagatcatcg gtgatgaagt gggcttgagg acacctcaga 420

gattcactga cctagtgaag ttcatctctg acaagattaa attccttaat ccggacaggg 480

aatacgactt cagagatctc acttggtgta tcaacccgcc agagagaatc aaattggatt 540

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atgatcaata ctgtgcagat gtggctgctg aagaactcat gaatgcattg gtgaactcaa 600

ctctactgga gaccagggca accaatcagt tcctagctgt ctcaaaggga aactgctcag 660

ggcccactac aatcagaggc caattctcaa acatgtcgct gtccctgttg gacttgtatt 720

taagtcgagg ttacaatgtg tcatctatag tcactatgac atcccaggga atgtacgggg 780

gaacttacct agtggaaaag cctaatctga gcagcaaagg gtcagagttg tcacaactga 840

gcatgcaccg agtgtttgaa gtaggtgtta tcagaaatcc gggtttgggg gctccggtat 900

tccatatgac aaactatctt gagcaaccag tcagtaatga tttcagcaac tgcatggtgg 960

ctttgggggga gctcaagttc gcagccctct gtcacaggga agattctatc acaattccct 1020

atcagggatc agggaaaggt gtcagcttcc agcttgtcaa gctaggtgtc tggaaatccc 1080

caaccgacat gcaatcctgg gtccccctat caacggatga tccagtgata gacaggcttt 1140

acctctcatc tcacagaggc gttatcgctg acaatcaagc aaaatgggct gtcccgacaa 1200

cacggacaga tgacaagttg cgaatggaga catgcttcca gcaggcgtgt aagggtaaaa 1260

tccaagcact ttgcgagaat cccgagtgga caccattgaa ggataacagg attccttcat 1320

acggggtctt gtctgttgat ctgagtctga cagttgagct taaaatcaaa attgtttcag 1380

gattcgggcc attgatcaca cacggttcag ggatggacct atacaaatcc aaccacaaca 1440

atatgtattg gctgactatc ccgccaatga agaacctggc cttaggtgta atcaacacat 1500

tggagtggat accgagattc aaggttagtc ccaacctctt cactgttcca attaaggaag 1560

caggcgagga ctgccatgcc ccaacatacc tacctgcgga ggtggatggt gatgtcaaac 1620

tcagttccaa tctggtgatt ctacctggtc aagatctcca atatgttctg gcaacctacg 1680

atacttccag agttgaacat gctgtagttt attacgttta cagcccaagc cgctcatttt 1740

cttacttttа tccttttagg ttgcctgtaa ggggggtccc cattgaatta caagtggaat 1800

gcttcacatg ggaccaaaaa ctctggtgcc gtcacttctg tgtgcttgcg gactcagaat 1860

ctggtggaca tatcactcac tctgggatgg tgggcatggg agtcagctgc acagccactc 1920

gggaagatgg aaccagccgc agatagtgat aataggctgg agcctcggtg gccaagcttc 1980

ttgccccttg ggcctccccc cagcccctcc tccccttcct gcacccgtac ccccgtggtc 2040

tttgaataaa gtctgagtgg gcggc 2065

<210> SEQ ID NO 45
<211> LENGTH: 1854
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 45

atgtcaccac aacgagaccg gataaatgcc ttctacaaag acaacccccа tcctaaggga 60

agtaggatag ttattaacag agaacatctt atgattgata gaccttatgt tttgctggct 120

gttctattcg tcatgtttct gagcttgatc gggttgctag ccattgcagg cattagactt 180

catcgggcag ccatctacac cgcagagatc cataaaagcc tcagcaccaa tctggatgta 240

actaactcaa tcgagcatca ggttaaggac gtgctgacac cactcttcaa gatcatcggt 300

gatgaagtgg gcttgaggac acctcagaga ttcactgacc tagtgaagtt catctctgac 360

aagattaaat tccttaatcc ggacagggaa tacgacttca gagatctcac ttggtgtatc 420

aacccgccag agagaatcaa attggattat gatcaatact gtgcagatgt ggctgctgaa 480

-continued

gaactcatga atgcattggt gaactcaact ctactggaga ccagggcaac caatcagttc 540

ctagctgtct caaagggaaa ctgctcaggg cccactacaa tcagaggcca attctcaaac 600

atgtcgctgt ccctgttgga cttgtattta agtcgaggtt acaatgtgtc atctatagtc 660

actatgacat cccagggaat gtacgggggа acttacctag tggaaaagcc taatctgagc 720

agcaaagggt cagagttgtc acaactgagc atgcaccgag tgtttgaagt aggtgttatc 780

agaaatccgg gtttgggggc tccggtattc catatgacaa actatcttga gcaaccagtc 840

agtaatgatt tcagcaactg catggtggct ttgggggagc tcaagttcgc agccctctgt 900

cacagggaag attctatcac aattccctat cagggatcag ggaaaggtgt cagcttccag 960

cttgtcaagc taggtgtctg gaaatcccca accgacatgc aatcctgggt ccccctatca 1020

acggatgatc cagtgataga caggctttac ctctcatctc acagaggcgt tatcgctgac 1080

aatcaagcaa aatgggctgt cccgacaaca cggacagatg acaagttgcg aatggagaca 1140

tgcttccagc aggcgtgtaa gggtaaaatc caagcacttt gcgagaatcc cgagtggaca 1200

ccattgaagg ataacaggat tccttcatac ggggtcttgt ctgttgatct gagtctgaca 1260

gttgagctta aaatcaaaat tgtttcagga ttcgggccat tgatcacaca cggttcaggg 1320

atggacctat acaaatccaa ccacaacaat atgtattggc tgactatccc gccaatgaag 1380

aacctggcct taggtgtaat caacacattg gagtggatac cgagattcaa ggttagtccc 1440

aacctcttca ctgttccaat taaggaagca ggcgaggact gccatgcccc aacataccta 1500

cctgcggagg tggatggtga tgtcaaactc agttccaatc tggtgattct acctggtcaa 1560

gatctccaat atgttctggc aacctacgat acttccagag ttgaacatgc tgtagtttat 1620

tacgtttaca gcccaagccg ctcatttttct tacttttatc cttttaggtt gcctgtaagg 1680

ggggtcccca ttgaattaca agtggaatgc ttcacatggg accaaaaact ctggtgccgt 1740

cacttctgtg tgcttgcgga ctcagaatct ggtggacata tcactcactc tgggatggtg 1800

ggcatgggag tcagctgcac agccactcgg gaagatggaa ccagccgcag atag 1854

<210> SEQ ID NO 46
<211> LENGTH: 2126
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 46

ggggaaataa gagagaaaag aagagtaaga agaaatataa gagccaccat gtcaccacaa 60

cgagaccgga taaatgcctt ctacaaagac aacccccatc ctaagggaag taggatagtt 120

attaacagag aacatcttat gattgataga ccttatgttt tgctggctgt tctattcgtc 180

atgtttctga gcttgatcgg gttgctagcc attgcaggca ttagacttca tcgggcagcc 240

atctacaccg cagagatcca taaaagcctc agcaccaatc tggatgtaac taactcaatc 300

gagcatcagg ttaaggacgt gctgacacca ctcttcaaga tcatcggtga tgaagtgggc 360

ttgaggacac ctcagagatt cactgaccta gtgaagttca tctctgacaa gattaaattc 420

cttaatccgg acagggaata cgacttcaga gatctcactt ggtgtatcaa cccgccagag 480

agaatcaaat tggattatga tcaatactgt gcagatgtgg ctgctgaaga actcatgaat 540

gcattggtga actcaactct actggagacc agggcaacca atcagttcct agctgtctca 600

aagggaaact gctcagggcc cactacaatc agaggccaat tctcaaacat gtcgctgtcc 660

ctgttggact tgtatttaag tcgaggttac aatgtgtcat ctatagtcac tatgacatcc 720

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cagggaatgt acgggggaac ttacctagtg gaaaagccta atctgagcag caaagggtca    780

gagttgtcac aactgagcat gcaccgagtg tttgaagtag gtgttatcag aaatccgggt    840

ttgggggctc cggtattcca tatgacaaac tatcttgagc aaccagtcag taatgatttc    900

agcaactgca tggtggcttt gggggagctc aagttcgcag ccctctgtca cagggaagat    960

tctatcacaa ttccctatca gggatcaggg aaaggtgtca gcttccagct tgtcaagcta   1020

ggtgtctgga aatccccaac cgacatgcaa tcctgggtcc ccctatcaac ggatgatcca   1080

gtgatagaca ggctttacct ctcatctcac agaggcgtta tcgctgacaa tcaagcaaaa   1140

tgggctgtcc cgacaacacg gacagatgac aagttgcgaa tggagacatg cttccagcag   1200

gcgtgtaagg gtaaaatcca agcactttgc gagaatcccg agtggacacc attgaaggat   1260

aacaggattc cttcatacgg ggtcttgtct gttgatctga gtctgacagt tgagcttaaa   1320

atcaaaattg tttcaggatt cgggccattg atcacacacg gttcagggat ggacctatac   1380

aaatccaacc acaacaatat gtattggctg actatcccgc caatgaagaa cctggcctta   1440

ggtgtaatca acacattgga gtggataccg agattcaagg ttagtcccaa cctcttcact   1500

gttccaatta aggaagcagg cgaggactgc catgccccaa catacctacc tgcggaggtg   1560

gatggtgatg tcaaactcag ttccaatctg gtgattctac ctggtcaaga tctccaatat   1620

gttctggcaa cctacgatac ttccagagtt gaacatgctg tagtttatta cgtttacagc   1680

ccaagccgct cattttctta cttttatcct tttaggttgc ctgtaagggg ggtccccatt   1740

gaattacaag tggaatgctt cacatgggac caaaaactct ggtgccgtca cttctgtgtg   1800

cttgcggact cagaatctgg tggacatatc actcactctg ggatggtggg catgggagtc   1860

agctgcacag ccactcggga agatggaacc agccgcagat agtgataata ggctggagcc   1920

tcggtggcca agcttcttgc cccttgggcc tccccccagc ccctcctccc cttcctgcac   1980

ccgtaccccc gtggtctttg aataaagtct gagtgggcgg caaaaaaaaa aaaaaaaaaa   2040

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa   2100

aaaaaaaaaa aaaaaaaaaa atctag                                        2126


<210> SEQ ID NO 47
<211> LENGTH: 550
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 47

Met Gly Leu Lys Val Asn Val Ser Ala Val Phe Met Ala Val Leu Leu
1               5                   10                  15

Thr Leu Gln Thr Pro Ala Gly Gln Ile His Trp Gly Asn Leu Ser Lys
            20                  25                  30

Ile Gly Val Val Gly Ile Gly Ser Ala Ser Tyr Lys Val Met Thr Arg
        35                  40                  45

Ser Ser His Gln Ser Leu Val Ile Lys Leu Met Pro Asn Ile Thr Leu
    50                  55                  60

Leu Asn Asn Cys Thr Arg Val Glu Ile Ala Glu Tyr Arg Arg Leu Leu
65                  70                  75                  80

Arg Thr Val Leu Glu Pro Ile Arg Asp Ala Leu Asn Ala Met Thr Gln
                85                  90                  95

Asn Ile Arg Pro Val Gln Ser Val Ala Ser Ser Arg Arg His Lys Arg
            100                 105                 110
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Phe Ala Gly Val Val Leu Ala Gly Ala Ala Leu Gly Val Ala Thr Ala
        115                 120                 125

Ala Gln Ile Thr Ala Gly Ile Ala Leu His Arg Ser Met Leu Asn Ser
    130                 135                 140

Gln Ala Ile Asp Asn Leu Arg Ala Ser Leu Glu Thr Thr Asn Gln Ala
145                 150                 155                 160

Ile Glu Ala Ile Arg Gln Ala Gly Gln Glu Met Ile Leu Ala Val Gln
                165                 170                 175

Gly Val Gln Asp Tyr Ile Asn Asn Glu Leu Ile Pro Ser Met Asn Gln
            180                 185                 190

Leu Ser Cys Asp Leu Ile Gly Gln Lys Leu Gly Leu Lys Leu Leu Arg
        195                 200                 205

Tyr Tyr Thr Glu Ile Leu Ser Leu Phe Gly Pro Ser Leu Arg Asp Pro
    210                 215                 220

Ile Ser Ala Glu Ile Ser Ile Gln Ala Leu Ser Tyr Ala Leu Gly Gly
225                 230                 235                 240

Asp Ile Asn Lys Val Leu Glu Lys Leu Gly Tyr Ser Gly Gly Asp Leu
                245                 250                 255

Leu Gly Ile Leu Glu Ser Arg Gly Ile Lys Ala Arg Ile Thr His Val
            260                 265                 270

Asp Thr Glu Ser Tyr Phe Ile Val Leu Ser Ile Ala Tyr Pro Thr Leu
        275                 280                 285

Ser Glu Ile Lys Gly Val Ile Val His Arg Leu Glu Gly Val Ser Tyr
    290                 295                 300

Asn Ile Gly Ser Gln Glu Trp Tyr Thr Thr Val Pro Lys Tyr Val Ala
305                 310                 315                 320

Thr Gln Gly Tyr Leu Ile Ser Asn Phe Asp Glu Ser Ser Cys Thr Phe
                325                 330                 335

Met Pro Glu Gly Thr Val Cys Ser Gln Asn Ala Leu Tyr Pro Met Ser
            340                 345                 350

Pro Leu Leu Gln Glu Cys Leu Arg Gly Ser Thr Lys Ser Cys Ala Arg
        355                 360                 365

Thr Leu Val Ser Gly Ser Phe Gly Asn Arg Phe Ile Leu Ser Gln Gly
    370                 375                 380

Asn Leu Ile Ala Asn Cys Ala Ser Ile Leu Cys Lys Cys Tyr Thr Thr
385                 390                 395                 400

Gly Thr Ile Ile Asn Gln Asp Pro Asp Lys Ile Leu Thr Tyr Ile Ala
                405                 410                 415

Ala Asp Arg Cys Pro Val Val Glu Val Asn Gly Val Thr Ile Gln Val
            420                 425                 430

Gly Ser Arg Arg Tyr Pro Asp Ala Val Tyr Leu His Arg Ile Asp Leu
        435                 440                 445

Gly Pro Pro Ile Ser Leu Glu Arg Leu Asp Val Gly Thr Asn Leu Gly
    450                 455                 460

Asn Ala Ile Ala Lys Leu Glu Asp Ala Lys Glu Leu Leu Glu Ser Ser
465                 470                 475                 480

Asp Gln Ile Leu Arg Ser Met Lys Gly Leu Ser Ser Thr Ser Ile Val
                485                 490                 495

Tyr Ile Leu Ile Ala Val Cys Leu Gly Gly Leu Ile Gly Ile Pro Thr
            500                 505                 510

Leu Ile Cys Cys Cys Arg Gly Arg Cys Asn Lys Lys Gly Glu Gln Val
        515                 520                 525
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Gly Met Ser Arg Pro Gly Leu Lys Pro Asp Leu Thr Gly Thr Ser Lys
    530                 535                 540

Ser Tyr Val Arg Ser Leu
545                 550


<210> SEQ ID NO 48
<211> LENGTH: 550
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 48

Met Gly Leu Lys Val Asn Val Ser Val Ile Phe Met Ala Val Leu Leu
1               5                   10                  15

Thr Leu Gln Thr Pro Thr Gly Gln Ile His Trp Gly Asn Leu Ser Lys
            20                  25                  30

Ile Gly Val Val Gly Val Gly Ser Ala Ser Tyr Lys Val Met Thr Arg
        35                  40                  45

Ser Ser His Gln Ser Leu Val Ile Lys Leu Met Pro Asn Ile Thr Leu
    50                  55                  60

Leu Asn Asn Cys Thr Arg Val Gly Ile Ala Glu Tyr Arg Arg Leu Leu
65                  70                  75                  80

Arg Thr Val Leu Glu Pro Ile Arg Asp Ala Leu Asn Ala Met Thr Gln
                85                  90                  95

Asn Ile Arg Pro Val Gln Ser Val Ala Ser Ser Arg Arg His Lys Arg
            100                 105                 110

Phe Ala Gly Val Val Leu Ala Gly Ala Ala Leu Gly Val Ala Thr Ala
        115                 120                 125

Ala Gln Ile Thr Ala Gly Ile Ala Leu His Gln Ser Met Leu Asn Ser
    130                 135                 140

Gln Ala Ile Asp Asn Leu Arg Ala Ser Leu Glu Thr Thr Asn Gln Ala
145                 150                 155                 160

Ile Glu Ala Ile Arg Gln Ala Gly Gln Glu Met Ile Leu Ala Val Gln
                165                 170                 175

Gly Val Gln Asp Tyr Ile Asn Asn Glu Leu Ile Pro Ser Met Asn Gln
            180                 185                 190

Leu Ser Cys Asp Leu Ile Gly Gln Lys Leu Gly Leu Lys Leu Leu Arg
        195                 200                 205

Tyr Tyr Thr Glu Ile Leu Ser Leu Phe Gly Pro Ser Leu Arg Asp Pro
    210                 215                 220

Ile Ser Ala Glu Ile Ser Ile Gln Ala Leu Ser Tyr Ala Leu Gly Gly
225                 230                 235                 240

Asp Ile Asn Lys Val Leu Glu Lys Leu Gly Tyr Ser Gly Gly Asp Leu
                245                 250                 255

Leu Gly Ile Leu Glu Ser Arg Gly Ile Lys Ala Arg Ile Thr His Val
            260                 265                 270

Asp Thr Glu Ser Tyr Phe Ile Val Leu Ser Ile Ala Tyr Pro Thr Leu
        275                 280                 285

Ser Glu Ile Lys Gly Val Ile Val His Arg Leu Glu Gly Val Ser Tyr
    290                 295                 300

Asn Ile Gly Ser Gln Glu Trp Tyr Thr Thr Val Pro Lys Tyr Val Ala
305                 310                 315                 320

Thr Gln Gly Tyr Leu Ile Ser Asn Phe Asp Glu Ser Ser Cys Thr Phe
                325                 330                 335
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Met Pro Glu Gly Thr Val Cys Ser Gln Asn Ala Leu Tyr Pro Met Ser
340 345 350

Pro Leu Leu Gln Glu Cys Leu Arg Gly Ser Thr Lys Ser Cys Ala Arg
355 360 365

Thr Leu Val Ser Gly Ser Phe Gly Asn Arg Phe Ile Leu Ser Gln Gly
370 375 380

Asn Leu Ile Ala Asn Cys Ala Ser Ile Leu Cys Lys Cys Tyr Thr Thr
385 390 395 400

Gly Thr Ile Ile Asn Gln Asp Pro Asp Lys Ile Leu Thr Tyr Ile Ala
405 410 415

Ala Asp His Cys Pro Val Val Glu Val Asn Gly Val Thr Ile Gln Val
420 425 430

Gly Ser Arg Arg Tyr Pro Asp Ala Val Tyr Leu His Arg Ile Asp Leu
435 440 445

Gly Pro Pro Ile Ser Leu Glu Arg Leu Asp Val Gly Thr Asn Leu Gly
450 455 460

Asn Ala Ile Ala Lys Leu Glu Asp Ala Lys Glu Leu Leu Glu Ser Ser
465 470 475 480

Asp Gln Ile Leu Arg Ser Met Lys Gly Leu Ser Ser Thr Ser Ile Val
485 490 495

Tyr Ile Leu Ile Ala Val Cys Leu Gly Gly Leu Ile Gly Ile Pro Ala
500 505 510

Leu Ile Cys Cys Cys Arg Gly Arg Cys Asn Lys Lys Gly Glu Gln Val
515 520 525

Gly Met Ser Arg Pro Gly Leu Lys Pro Asp Leu Thr Gly Thr Ser Lys
530 535 540

Ser Tyr Val Arg Ser Leu
545 550

<210> SEQ ID NO 49
<211> LENGTH: 617
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 49

Met Ser Pro Gln Arg Asp Arg Ile Asn Ala Phe Tyr Lys Asp Asn Pro
1 5 10 15

Tyr Pro Lys Gly Ser Arg Ile Val Ile Asn Arg Glu His Leu Met Ile
20 25 30

Asp Arg Pro Tyr Val Leu Leu Ala Val Leu Phe Val Met Phe Leu Ser
35 40 45

Leu Ile Gly Leu Leu Ala Ile Ala Gly Ile Arg Leu His Arg Ala Ala
50 55 60

Ile Tyr Thr Ala Glu Ile His Lys Ser Leu Ser Thr Asn Leu Asp Val
65 70 75 80

Thr Asn Ser Ile Glu His Gln Val Lys Asp Val Leu Thr Pro Leu Phe
85 90 95

Lys Ile Ile Gly Asp Glu Val Gly Leu Arg Thr Pro Gln Arg Phe Thr
100 105 110

Asp Leu Val Lys Phe Ile Ser Asp Lys Ile Lys Phe Leu Asn Pro Asp
115 120 125

Arg Glu Tyr Asp Phe Arg Asp Leu Thr Trp Cys Ile Asn Pro Pro Glu
130 135 140

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Arg Ile Lys Leu Asp Tyr Asp Gln Tyr Cys Ala Asp Val Ala Ala Glu
145                 150                 155                 160

Glu Leu Met Asn Ala Leu Val Asn Ser Thr Leu Leu Glu Thr Arg Thr
                165                 170                 175

Thr Thr Gln Phe Leu Ala Val Ser Lys Gly Asn Cys Ser Gly Pro Thr
            180                 185                 190

Thr Ile Arg Gly Gln Phe Ser Asn Met Ser Leu Ser Leu Leu Asp Leu
        195                 200                 205

Tyr Leu Gly Arg Gly Tyr Asn Val Ser Ser Ile Val Thr Met Thr Ser
    210                 215                 220

Gln Gly Met Tyr Gly Gly Thr Tyr Leu Val Glu Lys Pro Asn Leu Asn
225                 230                 235                 240

Ser Lys Gly Ser Glu Leu Ser Gln Leu Ser Met Tyr Arg Val Phe Glu
                245                 250                 255

Val Gly Val Ile Arg Asn Pro Gly Leu Gly Ala Pro Val Phe His Met
            260                 265                 270

Thr Asn Tyr Phe Glu Gln Pro Val Ser Asn Gly Leu Gly Asn Cys Met
        275                 280                 285

Val Ala Leu Gly Glu Leu Lys Leu Ala Ala Leu Cys His Gly Asp Asp
    290                 295                 300

Ser Ile Ile Ile Pro Tyr Gln Gly Ser Gly Lys Gly Val Ser Phe Gln
305                 310                 315                 320

Leu Val Lys Leu Gly Val Trp Lys Ser Pro Thr Asp Met Gln Ser Trp
                325                 330                 335

Val Pro Leu Ser Thr Asp Asp Pro Val Val Asp Arg Leu Tyr Leu Ser
            340                 345                 350

Ser His Arg Gly Val Ile Ala Asp Asn Gln Ala Lys Trp Ala Val Pro
        355                 360                 365

Thr Thr Arg Thr Asp Asp Lys Leu Arg Met Glu Thr Cys Phe Gln Gln
    370                 375                 380

Ala Cys Lys Gly Lys Ile Gln Ala Leu Cys Glu Asn Pro Glu Trp Val
385                 390                 395                 400

Pro Leu Lys Asp Asn Arg Ile Pro Ser Tyr Gly Val Leu Ser Val Asp
                405                 410                 415

Leu Ser Leu Thr Val Glu Leu Lys Ile Lys Ile Ala Ser Gly Phe Gly
            420                 425                 430

Pro Leu Ile Thr His Gly Ser Gly Met Asp Leu Tyr Lys Ser Asn Cys
        435                 440                 445

Asn Asn Val Tyr Trp Leu Thr Ile Pro Pro Met Arg Asn Leu Ala Leu
    450                 455                 460

Gly Val Ile Asn Thr Leu Glu Trp Ile Pro Arg Phe Lys Val Ser Pro
465                 470                 475                 480

Asn Leu Phe Thr Val Pro Ile Lys Glu Ala Gly Glu Asp Cys His Ala
                485                 490                 495

Pro Thr Tyr Leu Pro Ala Glu Val Asp Gly Asp Val Lys Leu Ser Ser
            500                 505                 510

Asn Leu Val Ile Leu Pro Gly Gln Asp Leu Gln Tyr Val Leu Ala Thr
        515                 520                 525

Tyr Asp Thr Ser Arg Val Glu His Ala Val Val Tyr Tyr Val Tyr Ser
    530                 535                 540

Pro Ser Arg Ser Phe Ser Tyr Phe Tyr Pro Phe Arg Leu Pro Ile Lys
545                 550                 555                 560

Gly Val Pro Ile Glu Leu Gln Val Glu Cys Phe Thr Trp Asp Gln Lys
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               565                 570                 575

Leu Trp Cys Arg His Phe Cys Val Leu Ala Asp Ser Glu Ser Gly Gly
            580                 585                 590

Leu Ile Thr His Ser Gly Met Val Gly Met Gly Val Ser Cys Thr Ala
        595                 600                 605

Thr Arg Glu Asp Gly Thr Asn Arg Arg
    610                 615


<210> SEQ ID NO 50
<211> LENGTH: 617
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 50

Met Ser Pro Gln Arg Asp Arg Ile Asn Ala Phe Tyr Lys Asp Asn Pro
1               5                   10                  15

His Pro Lys Gly Ser Arg Ile Val Ile Asn Arg Glu His Leu Met Ile
            20                  25                  30

Asp Arg Pro Tyr Val Leu Leu Ala Val Leu Phe Val Met Phe Leu Ser
        35                  40                  45

Leu Ile Gly Leu Leu Ala Ile Ala Gly Ile Arg Leu His Arg Ala Ala
    50                  55                  60

Ile Tyr Thr Ala Glu Ile His Lys Ser Leu Ser Thr Asn Leu Asp Val
65                  70                  75                  80

Thr Asn Ser Ile Glu His Gln Val Lys Asp Val Leu Thr Pro Leu Phe
                85                  90                  95

Lys Ile Ile Gly Asp Glu Val Gly Leu Arg Thr Pro Gln Arg Phe Thr
            100                 105                 110

Asp Leu Val Lys Phe Ile Ser Asp Lys Ile Lys Phe Leu Asn Pro Asp
        115                 120                 125

Arg Glu Tyr Asp Phe Arg Asp Leu Thr Trp Cys Ile Asn Pro Pro Glu
    130                 135                 140

Arg Ile Lys Leu Asp Tyr Asp Gln Tyr Cys Ala Asp Val Ala Ala Glu
145                 150                 155                 160

Glu Leu Met Asn Ala Leu Val Asn Ser Thr Leu Leu Glu Thr Arg Ala
                165                 170                 175

Thr Asn Gln Phe Leu Ala Val Ser Lys Gly Asn Cys Ser Gly Pro Thr
            180                 185                 190

Thr Ile Arg Gly Gln Phe Ser Asn Met Ser Leu Ser Leu Leu Asp Leu
        195                 200                 205

Tyr Leu Ser Arg Gly Tyr Asn Val Ser Ser Ile Val Thr Met Thr Ser
    210                 215                 220

Gln Gly Met Tyr Gly Gly Thr Tyr Leu Val Glu Lys Pro Asn Leu Ser
225                 230                 235                 240

Ser Lys Gly Ser Glu Leu Ser Gln Leu Ser Met His Arg Val Phe Glu
                245                 250                 255

Val Gly Val Ile Arg Asn Pro Gly Leu Gly Ala Pro Val Phe His Met
            260                 265                 270

Thr Asn Tyr Leu Glu Gln Pro Val Ser Asn Asp Phe Ser Asn Cys Met
        275                 280                 285

Val Ala Leu Gly Glu Leu Lys Phe Ala Ala Leu Cys His Arg Glu Asp
    290                 295                 300

Ser Ile Thr Ile Pro Tyr Gln Gly Ser Gly Lys Gly Val Ser Phe Gln
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305                 310                 315                 320

Leu Val Lys Leu Gly Val Trp Lys Ser Pro Thr Asp Met Gln Ser Trp
                325                 330                 335

Val Pro Leu Ser Thr Asp Asp Pro Val Ile Asp Arg Leu Tyr Leu Ser
            340                 345                 350

Ser His Arg Gly Val Ile Ala Asp Asn Gln Ala Lys Trp Ala Val Pro
        355                 360                 365

Thr Thr Arg Thr Asp Asp Lys Leu Arg Met Glu Thr Cys Phe Gln Gln
    370                 375                 380

Ala Cys Lys Gly Lys Ile Gln Ala Leu Cys Glu Asn Pro Glu Trp Thr
385                 390                 395                 400

Pro Leu Lys Asp Asn Arg Ile Pro Ser Tyr Gly Val Leu Ser Val Asp
                405                 410                 415

Leu Ser Leu Thr Val Glu Leu Lys Ile Lys Ile Val Ser Gly Phe Gly
            420                 425                 430

Pro Leu Ile Thr His Gly Ser Gly Met Asp Leu Tyr Lys Ser Asn His
        435                 440                 445

Asn Asn Met Tyr Trp Leu Thr Ile Pro Pro Met Lys Asn Leu Ala Leu
    450                 455                 460

Gly Val Ile Asn Thr Leu Glu Trp Ile Pro Arg Phe Lys Val Ser Pro
465                 470                 475                 480

Asn Leu Phe Thr Val Pro Ile Lys Glu Ala Gly Glu Asp Cys His Ala
                485                 490                 495

Pro Thr Tyr Leu Pro Ala Glu Val Asp Gly Asp Val Lys Leu Ser Ser
            500                 505                 510

Asn Leu Val Ile Leu Pro Gly Gln Asp Leu Gln Tyr Val Leu Ala Thr
        515                 520                 525

Tyr Asp Thr Ser Arg Val Glu His Ala Val Val Tyr Tyr Val Tyr Ser
    530                 535                 540

Pro Ser Arg Ser Phe Ser Tyr Phe Tyr Pro Phe Arg Leu Pro Val Arg
545                 550                 555                 560

Gly Val Pro Ile Glu Leu Gln Val Glu Cys Phe Thr Trp Asp Gln Lys
                565                 570                 575

Leu Trp Cys Arg His Phe Cys Val Leu Ala Asp Ser Glu Ser Gly Gly
            580                 585                 590

His Ile Thr His Ser Gly Met Val Gly Met Gly Val Ser Cys Thr Ala
        595                 600                 605

Thr Arg Glu Asp Gly Thr Ser Arg Arg
    610                 615


<210> SEQ ID NO 51
<211> LENGTH: 1729
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 51

tcaagctttt ggaccctcgt acagaagcta atacgactca ctatagggaa ataagagaga     60

aaagaagagt aagaagaaat ataagagcca ccatggcaca agtcattaat acaaacagcc    120

tgtcgctgtt gacccagaat aacctgaaca aatcccagtc cgcactgggc actgctatcg    180

agcgtttgtc ttccggtctg cgtatcaaca gcgcgaaaga cgatgcggca ggacaggcga    240

ttgctaaccg ttttaccgcg aacatcaaag gtctgactca ggcttcccgt aacgctaacg    300
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acggtatctc cattgcgcag accactgaag gcgcgctgaa cgaaatcaac aacaacctgc 360

agcgtgtgcg tgaactggcg gttcagtctg cgaatggtac taactcccag tctgacctcg 420

actccatcca ggctgaaatc acccagcgcc tgaacgaaat cgaccgtgta tccggccaga 480

ctcagttcaa cggcgtgaaa gtcctggcgc aggacaacac cctgaccatc caggttggtg 540

ccaacgacgg tgaaactatc gatattgatt taaaagaaat cagctctaaa acactgggac 600

ttgataagct taatgtccaa gatgcctaca ccccgaaaga aactgctgta accgttgata 660

aaactaccta taaaaatggt acagatccta ttacagccca gagcaatact gatatccaaa 720

ctgcaattgg cggtggtgca acgggggtta ctggggctga tatcaaattt aaagatggtc 780

aatactattt agatgttaaa ggcggtgctt ctgctggtgt ttataaagcc acttatgatg 840

aaactacaaa gaaagttaat attgatacga ctgataaaac tccgttggca actgcggaag 900

ctacagctat tcggggaacg gccactataa cccacaacca aattgctgaa gtaacaaaag 960

agggtgttga tacgaccaca gttgcggctc aacttgctgc agcaggggtt actggcgccg 1020

ataaggacaa tactagcctt gtaaaactat cgtttgagga taaaaacggt aaggttattg 1080

atggtggcta tgcagtgaaa atgggcgacg atttctatgc cgctacatat gatgagaaaa 1140

caggtgcaat tactgctaaa accactactt atacagatgg tactggcgtt gctcaaactg 1200

gagctgtgaa atttggtggc gcaaatggta aatctgaagt tgttactgct accgatggta 1260

agacttactt agcaagcgac cttgacaaac ataacttcag aacaggcggt gagcttaaag 1320

aggttaatac agataagact gaaaacccac tgcagaaaat tgatgctgcc ttggcacagg 1380

ttgatacact tcgttctgac ctgggtgcgg ttcagaaccg tttcaactcc gctatcacca 1440

acctgggcaa taccgtaaat aacctgtctt ctgcccgtag ccgtatcgaa gattccgact 1500

acgcaaccga agtctccaac atgtctcgcg cgcagattct gcagcaggcc ggtacctccg 1560

ttctggcgca ggcgaaccag gttccgcaaa acgtcctctc tttactgcgt tgataatagg 1620

ctggagcctc ggtggccatg cttcttgccc cttgggcctc cccccagccc ctcctcccct 1680

tcctgcaccc gtacccccgt ggtctttgaa taaagtctga gtgggcggc 1729

<210> SEQ ID NO 52
<211> LENGTH: 1518
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 52

atggcacaag tcattaatac aaacagcctg tcgctgttga cccagaataa cctgaacaaa 60

tcccagtccg cactgggcac tgctatcgag cgtttgtctt ccggtctgcg tatcaacagc 120

gcgaaagacg atgcggcagg acaggcgatt gctaaccgtt ttaccgcgaa catcaaaggt 180

ctgactcagg cttcccgtaa cgctaacgac ggtatctcca ttgcgcagac cactgaaggc 240

gcgctgaacg aaatcaacaa caacctgcag cgtgtgcgtg aactggcggt tcagtctgcg 300

aatggtacta actcccagtc tgacctcgac tccatccagg ctgaaatcac ccagcgcctg 360

aacgaaatcg accgtgtatc cggccagact cagttcaacg gcgtgaaagt cctggcgcag 420

gacaacaccc tgaccatcca ggttggtgcc aacgacggtg aaactatcga tattgattta 480

aaagaaatca gctctaaaac actgggactt gataagctta atgtccaaga tgcctacacc 540

ccgaaagaaa ctgctgtaac cgttgataaa actacctata aaaatggtac agatcctatt 600

acagcccaga gcaatactga tatccaaact gcaattggcg gtggtgcaac gggggttact 660

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ggggctgata tcaaatttaa agatggtcaa tactatttag atgttaaagg cggtgcttct 720

gctggtgttt ataaagccac ttatgatgaa actacaaaga aagttaatat tgatacgact 780

gataaaactc cgttggcaac tgcggaagct acagctattc ggggaacggc cactataacc 840

cacaaccaaa ttgctgaagt aacaaaagag ggtgttgata cgaccacagt tgcggctcaa 900

cttgctgcag caggggttac tggcgccgat aaggacaata ctagccttgt aaaactatcg 960

tttgaggata aaaacggtaa ggttattgat ggtggctatg cagtgaaaat gggcgacgat 1020

ttctatgccg ctacatatga tgagaaaaca ggtgcaatta ctgctaaaac cactacttat 1080

acagatggta ctggcgttgc tcaaactgga gctgtgaaat ttggtggcgc aaatggtaaa 1140

tctgaagttg ttactgctac cgatggtaag acttacttag caagcgacct tgacaaacat 1200

aacttcagaa caggcggtga gcttaaagag gttaatacag ataagactga aaacccactg 1260

cagaaaattg atgctgcctt ggcacaggtt gatacacttc gttctgacct gggtgcggtt 1320

cagaaccgtt tcaactccgc tatcaccaac ctgggcaata ccgtaaataa cctgtcttct 1380

gcccgtagcc gtatcgaaga ttccgactac gcaaccgaag tctccaacat gtctcgcgcg 1440

cagattctgc agcaggccgg tacctccgtt ctggcgcagg cgaaccaggt tccgcaaaac 1500

gtcctctctt tactgcgt 1518

<210> SEQ ID NO 53
<211> LENGTH: 1790
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 53

ggggaaauaa gagagaaaag aagaguaaga agaaauauaa gagccaccau ggcacaaguc 60

auuaauacaa acagccuguc gcuguugacc cagaauaacc ugaacaaauc ccaguccgca 120

cugggcacug cuaucgagcg uuugucuucc ggucugcgua ucaacagcgc gaaagacgau 180

gcggcaggac aggcgauugc uaaccguuuu accgcgaaca ucaaaggucu gacucaggcu 240

ucccguaacg cuaacgacgg uaucuccauu gcgcagacca cugaaggcgc gcugaacgaa 300

aucaacaaca accugcagcg ugugcgugaa cuggcgguuc agucugcgaa ugguacuaac 360

ucccagucug accucgacuc cauccaggcu gaaaucaccc agcgccugaa cgaaaucgac 420

cguguauccg gccagacuca guucaacggc gugaaagucc uggcgcagga caacacccug 480

accauccagg uuggugccaa cgacggugaa acuaucgaua uugauuuaaa agaaaucagc 540

ucuaaaacac ugggacuuga uaagcuuaau guccaagaug ccuacacccc gaaagaaacu 600

gcuguaaccg uugauaaaac uaccuauaaa aaugguacag auccuauuac agcccagagc 660

aauacugaua uccaaacugc aauuggcggu ggugcaacgg ggguuacugg ggcugauauc 720

aaauuuaaag auggucaaua cuauuuagau guuaaaggcg gugcuucugc ugguguuuau 780

aaagccacuu augaugaaac uacaaagaaa guuaauauug auacgacuga uaaaacuccg 840

uuggcaacug cggaagcuac agcuauucgg ggaacggcca cuauaaccca caaccaaauu 900

gcugaaguaa caaaagaggg uguugauacg accacaguug cggcucaacu ugcugcagca 960

gggguuacug gcgccgauaa ggacaauacu agccuuguaa aacuaucguu ugaggauaaa 1020

aacgguaagg uuauugaugg uggcuaugca gugaaaaugg gcgacgauuu cuaugccgcu 1080

acauaugaug agaaaacagg ugcaauuacu gcuaaaacca cuacuuauac agaugguacu 1140

-continued

ggcguugcuc aaacuggagc ugugaaauuu gguggcgcaa augguaaauc ugaaguuguu 1200

acugcuaccg augguaagac uuacuuagca agcgaccuug acaaacauaa cuucagaaca 1260

ggcggugagc uuaaagaggu uaauacagau aagacugaaa acccacugca gaaaauugau 1320

gcugccuugg cacagguuga uacacuucgu ucugaccugg gugcgguuca gaaccguuuc 1380

aacuccgcua ucaccaaccu gggcaauacc guaaauaacc ugucuucugc ccguagccgu 1440

aucgaagauu ccgacuacgc aaccgaaguc uccaacaugu cucgcgcgca gauucugcag 1500

caggccggua ccuccguucu ggcgcaggcg aaccagguuc cgcaaaacgu ccucucuuua 1560

cugcguugau aauaggcugg agccucggug gccaugcuuc uugccccuug ggccucccc 1620

cagccccucc uccccuuccu gcacccguac ccccgugguc uuugaauaaa gucugagugg 1680

gcggcaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1740

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaucuag 1790

<210> SEQ ID NO 54
<211> LENGTH: 506
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 54

Met Ala Gln Val Ile Asn Thr Asn Ser Leu Ser Leu Leu Thr Gln Asn
1 5 10 15

Asn Leu Asn Lys Ser Gln Ser Ala Leu Gly Thr Ala Ile Glu Arg Leu
20 25 30

Ser Ser Gly Leu Arg Ile Asn Ser Ala Lys Asp Asp Ala Ala Gly Gln
35 40 45

Ala Ile Ala Asn Arg Phe Thr Ala Asn Ile Lys Gly Leu Thr Gln Ala
50 55 60

Ser Arg Asn Ala Asn Asp Gly Ile Ser Ile Ala Gln Thr Thr Glu Gly
65 70 75 80

Ala Leu Asn Glu Ile Asn Asn Asn Leu Gln Arg Val Arg Glu Leu Ala
85 90 95

Val Gln Ser Ala Asn Gly Thr Asn Ser Gln Ser Asp Leu Asp Ser Ile
100 105 110

Gln Ala Glu Ile Thr Gln Arg Leu Asn Glu Ile Asp Arg Val Ser Gly
115 120 125

Gln Thr Gln Phe Asn Gly Val Lys Val Leu Ala Gln Asp Asn Thr Leu
130 135 140

Thr Ile Gln Val Gly Ala Asn Asp Gly Glu Thr Ile Asp Ile Asp Leu
145 150 155 160

Lys Glu Ile Ser Ser Lys Thr Leu Gly Leu Asp Lys Leu Asn Val Gln
165 170 175

Asp Ala Tyr Thr Pro Lys Glu Thr Ala Val Thr Val Asp Lys Thr Thr
180 185 190

Tyr Lys Asn Gly Thr Asp Pro Ile Thr Ala Gln Ser Asn Thr Asp Ile
195 200 205

Gln Thr Ala Ile Gly Gly Gly Ala Thr Gly Val Thr Gly Ala Asp Ile
210 215 220

Lys Phe Lys Asp Gly Gln Tyr Tyr Leu Asp Val Lys Gly Gly Ala Ser
225 230 235 240

Ala Gly Val Tyr Lys Ala Thr Tyr Asp Glu Thr Thr Lys Lys Val Asn
245 250 255

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Ile Asp Thr Thr Asp Lys Thr Pro Leu Ala Thr Ala Glu Ala Thr Ala
            260                 265                 270

Ile Arg Gly Thr Ala Thr Ile Thr His Asn Gln Ile Ala Glu Val Thr
        275                 280                 285

Lys Glu Gly Val Asp Thr Thr Thr Val Ala Ala Gln Leu Ala Ala Ala
    290                 295                 300

Gly Val Thr Gly Ala Asp Lys Asp Asn Thr Ser Leu Val Lys Leu Ser
305                 310                 315                 320

Phe Glu Asp Lys Asn Gly Lys Val Ile Asp Gly Gly Tyr Ala Val Lys
                325                 330                 335

Met Gly Asp Asp Phe Tyr Ala Ala Thr Tyr Asp Glu Lys Thr Gly Ala
            340                 345                 350

Ile Thr Ala Lys Thr Thr Thr Tyr Thr Asp Gly Thr Gly Val Ala Gln
        355                 360                 365

Thr Gly Ala Val Lys Phe Gly Gly Ala Asn Gly Lys Ser Glu Val Val
    370                 375                 380

Thr Ala Thr Asp Gly Lys Thr Tyr Leu Ala Ser Asp Leu Asp Lys His
385                 390                 395                 400

Asn Phe Arg Thr Gly Gly Glu Leu Lys Glu Val Asn Thr Asp Lys Thr
                405                 410                 415

Glu Asn Pro Leu Gln Lys Ile Asp Ala Ala Leu Ala Gln Val Asp Thr
            420                 425                 430

Leu Arg Ser Asp Leu Gly Ala Val Gln Asn Arg Phe Asn Ser Ala Ile
        435                 440                 445

Thr Asn Leu Gly Asn Thr Val Asn Asn Leu Ser Ser Ala Arg Ser Arg
    450                 455                 460

Ile Glu Asp Ser Asp Tyr Ala Thr Glu Val Ser Asn Met Ser Arg Ala
465                 470                 475                 480

Gln Ile Leu Gln Gln Ala Gly Thr Ser Val Leu Ala Gln Ala Asn Gln
                485                 490                 495

Val Pro Gln Asn Val Leu Ser Leu Leu Arg
            500                 505


<210> SEQ ID NO 55
<211> LENGTH: 698
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 55

Met Ala Gln Val Ile Asn Thr Asn Ser Leu Ser Leu Leu Thr Gln Asn
1               5                   10                  15

Asn Leu Asn Lys Ser Gln Ser Ala Leu Gly Thr Ala Ile Glu Arg Leu
            20                  25                  30

Ser Ser Gly Leu Arg Ile Asn Ser Ala Lys Asp Asp Ala Ala Gly Gln
        35                  40                  45

Ala Ile Ala Asn Arg Phe Thr Ala Asn Ile Lys Gly Leu Thr Gln Ala
    50                  55                  60

Ser Arg Asn Ala Asn Asp Gly Ile Ser Ile Ala Gln Thr Thr Glu Gly
65                  70                  75                  80

Ala Leu Asn Glu Ile Asn Asn Asn Leu Gln Arg Val Arg Glu Leu Ala
                85                  90                  95

Val Gln Ser Ala Asn Ser Thr Asn Ser Gln Ser Asp Leu Asp Ser Ile
            100                 105                 110
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Gln Ala Glu Ile Thr Gln Arg Leu Asn Glu Ile Asp Arg Val Ser Gly
        115                 120                 125

Gln Thr Gln Phe Asn Gly Val Lys Val Leu Ala Gln Asp Asn Thr Leu
    130                 135                 140

Thr Ile Gln Val Gly Ala Asn Asp Gly Glu Thr Ile Asp Ile Asp Leu
145                 150                 155                 160

Lys Gln Ile Asn Ser Gln Thr Leu Gly Leu Asp Thr Leu Asn Val Gln
                165                 170                 175

Gln Lys Tyr Lys Val Ser Asp Thr Ala Ala Thr Val Thr Gly Tyr Ala
            180                 185                 190

Asp Thr Thr Ile Ala Leu Asp Asn Ser Thr Phe Lys Ala Ser Ala Thr
        195                 200                 205

Gly Leu Gly Gly Thr Asp Gln Lys Ile Asp Gly Asp Leu Lys Phe Asp
    210                 215                 220

Asp Thr Thr Gly Lys Tyr Tyr Ala Lys Val Thr Val Thr Gly Gly Thr
225                 230                 235                 240

Gly Lys Asp Gly Tyr Tyr Glu Val Ser Val Asp Lys Thr Asn Gly Glu
                245                 250                 255

Val Thr Leu Ala Gly Gly Ala Thr Ser Pro Leu Thr Gly Gly Leu Pro
            260                 265                 270

Ala Thr Ala Thr Glu Asp Val Lys Asn Val Gln Val Ala Asn Ala Asp
        275                 280                 285

Leu Thr Glu Ala Lys Ala Ala Leu Thr Ala Ala Gly Val Thr Gly Thr
    290                 295                 300

Ala Ser Val Val Lys Met Ser Tyr Thr Asp Asn Asn Gly Lys Thr Ile
305                 310                 315                 320

Asp Gly Gly Leu Ala Val Lys Val Gly Asp Asp Tyr Tyr Ser Ala Thr
                325                 330                 335

Gln Asn Lys Asp Gly Ser Ile Ser Ile Asn Thr Thr Lys Tyr Thr Ala
            340                 345                 350

Asp Asp Gly Thr Ser Lys Thr Ala Leu Asn Lys Leu Gly Gly Ala Asp
        355                 360                 365

Gly Lys Thr Glu Val Val Ser Ile Gly Gly Lys Thr Tyr Ala Ala Ser
    370                 375                 380

Lys Ala Glu Gly His Asn Phe Lys Ala Gln Pro Asp Leu Ala Glu Ala
385                 390                 395                 400

Ala Ala Thr Thr Thr Glu Asn Pro Leu Gln Lys Ile Asp Ala Ala Leu
                405                 410                 415

Ala Gln Val Asp Thr Leu Arg Ser Asp Leu Gly Ala Val Gln Asn Arg
            420                 425                 430

Phe Asn Ser Ala Ile Thr Asn Leu Gly Asn Thr Val Asn Asn Leu Thr
        435                 440                 445

Ser Ala Arg Ser Arg Ile Glu Asp Ser Asp Tyr Ala Thr Glu Val Ser
    450                 455                 460

Asn Met Ser Arg Ala Gln Ile Leu Gln Gln Ala Gly Thr Ser Val Leu
465                 470                 475                 480

Ala Gln Ala Asn Gln Val Pro Gln Asn Val Leu Ser Leu Leu Arg Gly
                485                 490                 495

Gly Gly Gly Ser Gly Gly Gly Gly Ser Met Met Ala Pro Asp Pro Asn
            500                 505                 510

Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn
        515                 520                 525
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Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn
    530                 535                 540

Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn
545                 550                 555                 560

Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn
                565                 570                 575

Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Lys Asn Asn Gln
            580                 585                 590

Gly Asn Gly Gln Gly His Asn Met Pro Asn Asp Pro Asn Arg Asn Val
        595                 600                 605

Asp Glu Asn Ala Asn Ala Asn Asn Ala Val Lys Asn Asn Asn Asn Glu
    610                 615                 620

Glu Pro Ser Asp Lys His Ile Glu Gln Tyr Leu Lys Lys Ile Lys Asn
625                 630                 635                 640

Ser Ile Ser Thr Glu Trp Ser Pro Cys Ser Val Thr Cys Gly Asn Gly
                645                 650                 655

Ile Gln Val Arg Ile Lys Pro Gly Ser Ala Asn Lys Pro Lys Asp Glu
            660                 665                 670

Leu Asp Tyr Glu Asn Asp Ile Glu Lys Lys Ile Cys Lys Met Glu Lys
        675                 680                 685

Cys Ser Ser Val Phe Asn Val Val Asn Ser
    690                 695


<210> SEQ ID NO 56
<211> LENGTH: 692
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 56

Met Met Ala Pro Asp Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala
1               5                   10                  15

Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala
            20                  25                  30

Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala
        35                  40                  45

Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala
    50                  55                  60

Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala
65                  70                  75                  80

Asn Pro Asn Lys Asn Asn Gln Gly Asn Gly Gln Gly His Asn Met Pro
                85                  90                  95

Asn Asp Pro Asn Arg Asn Val Asp Glu Asn Ala Asn Ala Asn Asn Ala
            100                 105                 110

Val Lys Asn Asn Asn Asn Glu Glu Pro Ser Asp Lys His Ile Glu Gln
        115                 120                 125

Tyr Leu Lys Lys Ile Lys Asn Ser Ile Ser Thr Glu Trp Ser Pro Cys
    130                 135                 140

Ser Val Thr Cys Gly Asn Gly Ile Gln Val Arg Ile Lys Pro Gly Ser
145                 150                 155                 160

Ala Asn Lys Pro Lys Asp Glu Leu Asp Tyr Glu Asn Asp Ile Glu Lys
                165                 170                 175

Lys Ile Cys Lys Met Glu Lys Cys Ser Ser Val Phe Asn Val Val Asn
            180                 185                 190
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Ser Arg Pro Val Thr Met Ala Gln Val Ile Asn Thr Asn Ser Leu Ser
        195                 200                 205

Leu Leu Thr Gln Asn Asn Leu Asn Lys Ser Gln Ser Ala Leu Gly Thr
    210                 215                 220

Ala Ile Glu Arg Leu Ser Ser Gly Leu Arg Ile Asn Ser Ala Lys Asp
225                 230                 235                 240

Asp Ala Ala Gly Gln Ala Ile Ala Asn Arg Phe Thr Ala Asn Ile Lys
                245                 250                 255

Gly Leu Thr Gln Ala Ser Arg Asn Ala Asn Asp Gly Ile Ser Ile Ala
            260                 265                 270

Gln Thr Thr Glu Gly Ala Leu Asn Glu Ile Asn Asn Asn Leu Gln Arg
        275                 280                 285

Val Arg Glu Leu Ala Val Gln Ser Ala Asn Ser Thr Asn Ser Gln Ser
    290                 295                 300

Asp Leu Asp Ser Ile Gln Ala Glu Ile Thr Gln Arg Leu Asn Glu Ile
305                 310                 315                 320

Asp Arg Val Ser Gly Gln Thr Gln Phe Asn Gly Val Lys Val Leu Ala
                325                 330                 335

Gln Asp Asn Thr Leu Thr Ile Gln Val Gly Ala Asn Asp Gly Glu Thr
            340                 345                 350

Ile Asp Ile Asp Leu Lys Gln Ile Asn Ser Gln Thr Leu Gly Leu Asp
        355                 360                 365

Thr Leu Asn Val Gln Gln Lys Tyr Lys Val Ser Asp Thr Ala Ala Thr
    370                 375                 380

Val Thr Gly Tyr Ala Asp Thr Thr Ile Ala Leu Asp Asn Ser Thr Phe
385                 390                 395                 400

Lys Ala Ser Ala Thr Gly Leu Gly Gly Thr Asp Gln Lys Ile Asp Gly
                405                 410                 415

Asp Leu Lys Phe Asp Asp Thr Thr Gly Lys Tyr Tyr Ala Lys Val Thr
            420                 425                 430

Val Thr Gly Gly Thr Gly Lys Asp Gly Tyr Tyr Glu Val Ser Val Asp
        435                 440                 445

Lys Thr Asn Gly Glu Val Thr Leu Ala Gly Gly Ala Thr Ser Pro Leu
    450                 455                 460

Thr Gly Gly Leu Pro Ala Thr Ala Thr Glu Asp Val Lys Asn Val Gln
465                 470                 475                 480

Val Ala Asn Ala Asp Leu Thr Glu Ala Lys Ala Ala Leu Thr Ala Ala
                485                 490                 495

Gly Val Thr Gly Thr Ala Ser Val Val Lys Met Ser Tyr Thr Asp Asn
            500                 505                 510

Asn Gly Lys Thr Ile Asp Gly Gly Leu Ala Val Lys Val Gly Asp Asp
        515                 520                 525

Tyr Tyr Ser Ala Thr Gln Asn Lys Asp Gly Ser Ile Ser Ile Asn Thr
    530                 535                 540

Thr Lys Tyr Thr Ala Asp Asp Gly Thr Ser Lys Thr Ala Leu Asn Lys
545                 550                 555                 560

Leu Gly Gly Ala Asp Gly Lys Thr Glu Val Val Ser Ile Gly Gly Lys
                565                 570                 575

Thr Tyr Ala Ala Ser Lys Ala Glu Gly His Asn Phe Lys Ala Gln Pro
            580                 585                 590

Asp Leu Ala Glu Ala Ala Ala Thr Thr Thr Glu Asn Pro Leu Gln Lys
        595                 600                 605

Ile Asp Ala Ala Leu Ala Gln Val Asp Thr Leu Arg Ser Asp Leu Gly
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    610                 615                 620

Ala Val Gln Asn Arg Phe Asn Ser Ala Ile Thr Asn Leu Gly Asn Thr
625                 630                 635                 640

Val Asn Asn Leu Thr Ser Ala Arg Ser Arg Ile Glu Asp Ser Asp Tyr
                645                 650                 655

Ala Thr Glu Val Ser Asn Met Ser Arg Ala Gln Ile Leu Gln Gln Ala
            660                 665                 670

Gly Thr Ser Val Leu Ala Gln Ala Asn Gln Val Pro Gln Asn Val Leu
        675                 680                 685

Ser Leu Leu Arg
    690
```

<210> SEQ ID NO 57
<211> LENGTH: 1620
<212> TYPE: RNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Human metapneumovirus

<400> SEQUENCE: 57

```
augagcugga agguggugau uaucuucagc cugcugauua caccucaaca cggccugaag     60

gagagcuacc uggaagagag cugcuccacc aucaccgagg gcuaccugag cgugcugcgg    120

accggcuggu acaccaacgu guucacccug gaggugggcg acguggagaa ccugaccugc    180

agcgacggcc cuagccugau caagaccgag cuggaccuga ccaagagcgc ucugagagag    240

cugaagaccg uguccgccga ccagcuggcc agagaggaac agaucgagaa cccucggcag    300

agcagauucg ugcugggcgc caucgcucug ggagucgccg cugccgcugc agugacagcu    360

ggaguggcca uugcuaagac caucagacug gaaagcgagg ugacagccau caacaaugcc    420

cugaagaaga ccaacgaggc cgugagcacc cugggcaaug gagugagagu gcuggccaca    480

gccgugcggg agcugaagga cuucgugagc aagaaccuga ccagagccau caacaagaac    540

aagugcgaca ucgaugaccu gaagauggcc gugagcuucu cccaguucaa cagacgguuc    600

cugaacgugg ugagacaguu cuccgacaac gcuggaauca caccugccau uagccuggac    660

cugaugaccg acgccgagcu ggcuagagcc gugcccaaca ugcccaccag cgcuggccag    720

aucaagcuga ugcuggagaa cagagccaug gugcggagaa agggcuucgg cauccugauu    780

gggguguaug gaagcuccgu gaucuacaug gugcagcugc ccaucuucgg cgugaucgac    840

acacccugcu ggaucgugaa ggccgcuccu agcugcuccg agaagaaagg aaacuaugcc    900

ugucugcuga gagaggacca gggcugguac ugccagaacg ccggaagcac aguguacuau    960

cccaacgaga aggacugcga gaccagaggc gaccacgugu ucugcgacac cgcugccgga   1020

aucaacgugg ccgagcagag caaggagugc aacaucaaca ucagcacaac caacuacccc   1080

ugcaagguga gcaccggacg gcaccccauc agcauggugg cucugagccc ucugggcgcu   1140

cugguggccu gcuauaaggg cguguccugu agcaucggca gcaaucgggu gggcaucauc   1200

aagcagcuga acaagggaug cuccuacauc accaaccagg acgccgacac cgugaccauc   1260

gacaacaccg uguaccagcu gagcaaggug gagggcgagc agcacgugau caagggcaga   1320

cccgugagcu ccagcuucga ccccaucaag uucccugagg accaguucaa cguggcccug   1380

gaccaggugu uugagaacau cgagaacagc caggcccugg uggaccagag caacagaauc   1440

cuguccagcg cugagaaggg caacaccggc uucaucauug ugaucauucu gaucgccgug   1500

cugggcagcu ccaugauccu ggugagcauc uucaucauua ucaagaagac caagaaaccc   1560
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accggagccc cuccugagcu gagcggcgug accaacaaug gcuucauucc ccacaacuga 1620

<210> SEQ ID NO 58
<211> LENGTH: 1620
<212> TYPE: RNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Human metapneumovirus

<400> SEQUENCE: 58

augucuugga aagugaugau caucauuucg uuacucauaa caccccagca cgggcuaaag 60

gagaguuauu uggaagaauc auguaguacu auaacugagg gauaccucag uguuuuaaga 120

acaggcuggu acacuaaugu cuucacauua gaaguuggug auguugaaaa ucuuacaugu 180

acugauggac cuagcuuaau caaaacagaa cuugaucuaa caaaaagugc uuuaagggaa 240

cucaaaacag ucucugcuga ucaguuggcg agagaggagc aaauugaaaa ucccagacaa 300

ucaagauuug ucuuaggugc gauagcucuc ggaguugcua cagcagcagc agucacagca 360

ggcauugcaa uagccaaaac cauaaggcuu gagagugagg ugaaugcaau uaaaggugcu 420

cucaaacaaa cuaaugaagc aguauccaca uuagggaaug gugugcgggu ccuagccacu 480

gcagugagag agcuaaaaga auuugugagc aaaaaccuga cuagugcaau caacaggaac 540

aaaugugaca uugcugaucu gaagauggcu gucagcuuca gucaauucaa cagaagauuu 600

cuaaauguug ugcggcaguu uucagacaau gcagggauaa caccagcaau aucauuggac 660

cugaugacug augcugaguu ggccagagcu guaucauaca ugccaacauc ugcagggcag 720

auaaaacuga uguuggagaa ccgcgcaaug guaaggagaa aaggauuugg aauccugaua 780

ggggucuacg gaagcucugu gauuuacaug guucaauugc cgaucuuugg ugucauagau 840

acaccuuguu ggaucaucaa ggcagcuccc ucuugcucag aaaaaaacgg gaauuaugcu 900

ugccuccuaa gagaggauca agggugguau uguaaaaaug caggaucuac uguuuacuac 960

ccaaaugaaa aagacugcga aacaagaggu gaucauguuu uuugugacac agcagcaggg 1020

aucaauguug cugagcaauc aagagaaugc aacaucaaca uaucuacuac caacuaccca 1080

ugcaaaguca gcacaggaag acacccuaua agcaugguug cacuaucacc ucucggugcu 1140

uugguggcuu gcuauaaagg gguaagcugc ucgauuggca gcaauugggu uggaaucauc 1200

aaacaauuac ccaaaggcug cucauacaua accaaccagg augcagacac uguaacaauu 1260

gacaauaccg uguaucaacu aagcaaaguu gaaggugaac agcauguaau aaaagggaga 1320

ccaguuucaa gcaguuuuga uccaaucaag uuuccugagg aucaguucaa uguugcgcuu 1380

gaucaagucu ucgaaagcau ugagaacagu caggcacuag uggaccaguc aaacaaaauu 1440

cuaaacagug cagaaaaagg aaacacuggu uucauuaucg uaguaauuuu gguugcuguu 1500

cuuggucuaa ccaugauuuc agugagcauc aucaucauaa ucaagaaaac aaggaagccc 1560

acaggagcac cuccagagcu gaaugguguc accaacggcg guuucauacc acauaguuag 1620

<210> SEQ ID NO 59
<211> LENGTH: 1620
<212> TYPE: RNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Human metapneumovirus

<400> SEQUENCE: 59

augucuugga aagugaugau uaucauuucg uuacucauaa caccucagca uggacuaaaa 60

gaaaguuauu uagaagaauc auguaguacu auaacugaag gauaucucag uguuuuaaga 120

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acagguuggu acaccaaugu cuuuacauua gaaguuggug auguugaaaa ucuuacaugu 180

acugauggac cuagcuuaau caaaacagaa cuugaccuaa ccaaaagugc uuuaagagaa 240

cucaaaacag uuucugcuga ucaguuagcg agagaagaac aaauugaaaa ucccagacaa 300

ucaagguuug uccuaggugc aauagcucuu ggaguugcca cagcagcagc agucacagca 360

ggcauugcaa uagccaaaac uauaaggcuu gagagugaag ugaaugcaau caaaggugcu 420

cucaaaacaa ccaaugaggc aguaucaaca cuaggaaaug gagugcgggu ccuagccacu 480

gcaguaagag agcugaaaga auuugugagc aaaaaccuga cuagugcgau caacaagaac 540

aagugugaca uugcugauuu gaagauggcu gucagcuuca gucaguucaa cagaagauuc 600

cuaaauguug ugcggcaguu uucagacaau gcagggauaa caccagcaau aucauuggac 660

cugaugaaug augcugagcu ggccagagcu guaucauaca ugccaacauc ugcaggacag 720

auaaaacuaa uguuagagaa ccgugcaaug gugaggagaa aaggauuugg aaucuugaua 780

ggggucuacg gaagcucugu gauuuacaug guccagcugc cgaucuuugg ugucauaaau 840

acaccuuguu ggauaaucaa ggcagcuccc ucuuguucag aaaaagaugg aaauuaugcu 900

ugccuccuaa gagaggauca aggugguau uguaaaaaug caggauccac uguuuacuac 960

ccaaaugaaa aagacugcga aacaagaggu gaucauguuu uuugugacac agcagcaggg 1020

aucaauguug cugagcaauc aagagaaugc aacaucaaca uaucuaccac caacuaccca 1080

ugcaaaguca gcacaggaag acacccuauc agcaugguug cacuaucacc ucucggugcu 1140

uugguagcuu gcuacaaagg gguuagcugc ucgacuggca guaaucaggu uggaauaauc 1200

aaacaacuac cuaaaggcug cucauacaua acuaaccagg acgcagacac uguaacaauu 1260

gacaacacug uguaucaacu aagcaaaguu gagggugaac agcauguaau aaaagggaga 1320

ccaguuucaa gcaguuuuga uccaaucagg uuuccugagg aucaguucaa uguugcgcuu 1380

gaucaagucu uugaaagcau ugaaaacagu caagcacuag uggaccaguc aaacaaaauu 1440

cugaacagug cagaaaaagg aaacacuggu uucauuauug uaauaauuuu gauugcuguu 1500

cuuggguuaa ccaugauuuc agugagcauc aucaucauaa ucaaaaaaac aaggaagccc 1560

acaggggcac cuccggagcu gaaugguguu accaacggcg guuucauacc gcauaguuag 1620

<210> SEQ ID NO 60
<211> LENGTH: 1725
<212> TYPE: RNA
<213> ORGANISM: Human respiratory syncytial virus

<400> SEQUENCE: 60

auggaguugc caauccucaa aacaaaugca auuaccacaa uccuugcugc agucacacuc 60

uguuucgcuu ccagucaaaa caucacugaa gaauuuuauc aaucaacaug cagugcaguu 120

agcaaaggcu aucuuagugc ucuaagaacu gguugguaua cuaguguuau aacuauagaa 180

uuaaguaaua ucaaggaaaa uaaguguaau ggaacagaug cuaagguaaa auugauaaaa 240

caagaauuag auaaauauaa aaaugcugua acagaauugc aguugcucau gcaaagcaca 300

ccagcagcca acaaucgagc cagaagagaa cuaccaaggu uuaugaauua uacacucaau 360

aauaccaaaa auaccaaugu aacauuaagc aagaaaagga aaagaagauu ucuuggcuuu 420

uuguuaggug uuggaucugc aaucgccagu ggcauugcug uaucuaaggu ccugcaccua 480

gaaggggaag ugaacaaaau caaaagugcu cuacuaucca caaacaaggc uguagucagc 540

uuaucaaaug gaguuagugu cuuaaccagc aaaguguuag accucaaaaa cuauauagau 600

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aaacaguugu uaccuauugu gaacaagcaa agcugcagca uaucaaacau ugaaacugug 660

auagaguucc aacaaaagaa caacagacua cuagagauua ccagggaauu uaguguuaau 720

gcagguguaa cuacaccugu aagcacuuau auguuaacua auagugaauu auuaucauua 780

aucaaugaua ugccuauaac aaaugaucag aaaaaguuaa uguccaacaa uguucaaaua 840

guuagacagc aaaguuacuc uaucaugucc auaauaaagg aggaagucuu agcauaugua 900

guacaauuac cacuauaugg uguaauagau acacccuguu ggaaacugca cacaccccu 960

cuauguacaa ccaacacaaa ggaagggucc aacaucugcu uaacaagaac cgacagagga 1020

ugguauugug acaaugcagg aucaguaucu uucuucccac aagcugaaac auguaaaguu 1080

caaucgaauc ggguauuuug ugacacaaug aacaguuuaa cauuaccaag ugaaguaaau 1140

cucugcaaca uugacauauu caaccccaaa uaugauugca aaauuaugac uucaaaaaca 1200

gauguaagca gcuccguuau cacaucucua ggagccauug ugucaugcua uggcaaaacu 1260

aaauguacag cauccaauaa aaaucguggg aucauaaaga cauuuucuaa cgggugugau 1320

uauguaucaa auaagggggu ggauacugug ucuguaggua auacauuaua uuauguaaau 1380

aagcaagaag gcaaaagucu cuauguaaaa ggugaaccaa uaauaaauuu cuaugaccca 1440

uuaguguucc ccucugauga auuugaugca ucaauaucuc aagucaauga gaagauuaac 1500

cagagccuag cauuuauucg uaaauccgau gaauuauuac auaauguaaa ugcugguaaa 1560

uccaccacaa auaucaugau aacuacuaua auuauaguga uuauaguaau auuguuauca 1620

uuaauugcag uuggacugcu ccuauacugc aaggccagaa gcacaccagu cacacuaagu 1680

aaggaucaac ugagugguau aaauaauauu gcauuuagua acuga 1725

<210> SEQ ID NO 61
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Human parainfluenza virus 3

<400> SEQUENCE: 61

augccaauuu caauacuguu aauuauuaca accaugauca uggcaucaca cugccaaaua 60

gacaucacaa aacuacagca uguaggugua uuggucaaca gucccaaagg gaugaagaua 120

ucacaaaacu ucgaaacaag auaucuaauc cugagucuca uaccaaaaau agaagauucu 180

aacucuugug gugaccaaca gaucaagcaa uacaagaggu uauuggauag acugaucauu 240

ccuuuauaug auggacuaag auuacagaag gaugugauag ugacuaauca agaauccaau 300

gaaaacacug aucccagaac agaacgauuc uuuggagggg uaauuggaac uauugcucua 360

ggaguagcaa ccucagcaca aauuacagca gcaguugcuc ugguugaagc caagcaggca 420

agaucagaca uugaaaaacu caaggaagca aucagggaca caaauaaagc agugcaguca 480

guucagagcu cuguaggaaa uuugauagua gcaauuaaau caguccagga uuaugucaac 540

aaagaaaucg ugccaucgau ugcgagacua gguugugaag cagcaggacu ucaguuaggg 600

auugcauuaa cacagcauua cucagaauua acaaauauau uuggugauaa cauaggaucg 660

uuacaagaaa aaggaauaaa auuacaaggu auagcaucau uauaccguac aaauaucaca 720

gaaauauuca caacaucaac aguugacaaa uaugauauuu augaucuauu auuuacagaa 780

ucaauaaagg ugagaguuau agauguugau uugaaugauu acucaauaac ccuccaaguc 840

agacucccuu uauugaccag acugcugaac acucaaaucu acaaaguaga uuccauauca 900

uacaauaucc aaaauagaga augguauauc ccucuuccca gccauaucau gacgaaaggg 960

gcauuucuag guggagcaga ugucaaagaa ugcauagaag cauucagcag uuauauaugc 1020

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ccuucugauc caggauuugu acuaaaccau gaaauggaga gcugucuauc aggaaacaua 1080

ucccaauguc caagaaccac agucacauca gacauaguuc cuagguaugc auuugucaau 1140

ggaggagugg uugcgaauug uauaacaacu acauguacau gcaaugguau cgguaauaga 1200

aucaaccaac caccugauca aggagucaaa auuauaacac auaaagaaug uaauacaaua 1260

gguaucaacg gaaugcuauu caacacaaac aaagaaggaa cucuugcauu cuacacacca 1320

gacgacauaa cauuaaacaa uucuguugca cuugauccga uugacauauc aaucgagcuc 1380

aacaaggcca aaucagaucu ugaggaauca aaagaaugga uaagaagguc aaaucaaaag 1440

cuagauucua uuggaaguug gcaucaaucu agcacuacaa ucauaguuau uuugauaaug 1500

augauuauau uguuuauaau uaauauaaca auaauuacaa uugcaauuaa guauuacaga 1560

auucaaaaga gaaaucgagu ggaucaaaau gauaagccgu auguauuaac aaacaag 1617

<210> SEQ ID NO 62
<211> LENGTH: 1716
<212> TYPE: RNA
<213> ORGANISM: Human parainfluenza virus 3

<400> SEQUENCE: 62

auggaauacu ggaagcacac caaccacgga aaggaugcug guaaugagcu ggagacaucc 60

acagccacuc auggcaacaa gcucaccaac aagauaacau auauauugug gacgauaacc 120

cugguguuau uaucaauagu cuucaucaua gugcuaacua auuccaucaa aagugaaaag 180

gcccgcgaau cauugcuaca agacauaaau aaugaguuua uggaaguuac agaaaagauc 240

caaguggcau cggauaauac uaaugaucua auacagucag gagugaauac aaggcuucuu 300

acaauucaga gucaugucca gaauuauaua ccaauaucau ugacacaaca aauaucggau 360

cuuaggaaau ucauuaguga aauuacaauu agaaaugaua aucaagaagu gccaccacaa 420

agaauaacac augauguggg uauaaaaccu uuaaauccag augauuucug gagaugcacg 480

ucuggucuuc caucuuugau gaaaacucca aaaauaagau uaaugccggg accaggauua 540

uuagcuaugc caacgacugu ugauggcugu gucagaaccc cguccuuagu gauaaaugau 600

cugauuuaug cuuacaccuc aaaucuaauu acucgagguu gccaggauau agggaaauca 660

uaucaaguau uacagauagg gauaauaacu guaaacucag acuugguacc ugacuuaaau 720

ccuaggaucu cucauaccuu caacauaaau gacaauagaa agucauguuc ucuagcacuc 780

cuaaauacag auguauauca acuguguuca accccaaaag uugaugaaag aucagauuau 840

gcaucaucag gcauagaaga uauuguacuu gauauuguca auuaugaugg cucaaucucg 900

acaacaagau uuaagaauaa uaauauaagu uuugaucaac cauaugcggc auuauaccca 960

ucuguuggac cagggauaua cuacaaaggc aaaauaauau uucucgggua uggaggucuu 1020

gaacauccaa uaaaugagaa ugcaaucugc aacacaacug gguguccugg gaaaacacag 1080

agagacugua aucaagcauc ucauagucca ugguuuucag auagaaggau ggucaacucu 1140

auaauuguug uugacaaggg cuugaacuca guuccaaaau ugaagguaug gacgauaucu 1200

augagacaaa auuacugggg gucagaagga agauuacuuc uacuagguaa caagaucuac 1260

auauacacaa gaucuacaag uuggcacagc aaguuacaau uaggaauaau ugacauuacu 1320

gacuacagug auauaaggau aaaauggaca uggcauaaug ugcuaucaag accaggaaac 1380

aaugaauguc caugggaca uucauguccg gauggaugua uaacgggagu auauaccgau 1440

gcauauccac ucaaucccac aggaagcauu guaucaucug ucauauugga cucacaaaaa 1500

-continued

ucgagaguca acccagucau aacuuacuca acagcaaccg aaaggguaaa cgagcuggcu 1560

auccgaaaca aaacacucuc agcuggguac acaacaacaa gcugcauuac acacuauaac 1620

aaaggguauu guuuucauau aguagaaaua aaucauaaaa gcuuaaacac auuucaaccc 1680

auguuguuca aaacagagau uccaaaaagc ugcagu 1716

<210> SEQ ID NO 63
<211> LENGTH: 1716
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 63

auggaauacu ggaagcacac caaccacggc aaggacgccg gcaacgagcu ggaaaccagc 60

acagccacac acggcaacaa gcugaccaac aagaucaccu acauccugug gaccaucacc 120

cuggugcugc ugagcaucgu guucaucauc gugcugacca auagcaucaa gagcgagaag 180

gccagagaga gccugcugca ggacaucaac aacgaguuca uggaagugac cgagaagauc 240

cagguggcca gcgacaacac caacgaccug auccagagcg gcgugaacac ccggcugcug 300

accauccaga gccacgugca gaacuacauc cccaucagcc ugacccagca gaucagcgac 360

cugcggaagu ucaucagcga gaucaccauc cggaacgaca accaggaagu gccccccag 420

agaaucaccc acgacguggg caucaagccc cugaaccccg acgauuucug gcgguguaca 480

agcggccugc ccagccugau gaagaccccc aagauccggc ugaugccugg cccuggacug 540

cuggccaugc cuaccacagu ggauggcugu gugcggaccc ccagccucgu gaucaacgau 600

cugaucuacg ccuacaccag caaccugauc acccggggcu gccaggauau cggcaagagc 660

uaccaggugc ugcagaucgg caucaucacc gugaacuccg accuggugcc cgaccugaac 720

ccucggauca gccacaccuu caacaucaac gacaacagaa agagcugcag ccuggcucug 780

cugaacaccg acguguacca gcugugcagc acccccaagg uggacgagag aagcgacuac 840

gccagcagcg gcaucgagga uaucgugcug gacaucguga acuacgacgg cagcaucagc 900

accacccggu ucaagaacaa caacaucagc uucgaccagc ccuacgccgc ccuguacccu 960

ucuguggggcc cuggcaucua cuacaagggc aagaucaucu uccugggcua cggcggccug 1020

gaacacccca ucaacgagaa cgccaucugc aacaccaccg gcugcccugg caagacccag 1080

agagacugca aucaggccag ccacagcccc ugguucagcg accgcagaau ggucaacucu 1140

aucaucgugg uggacaaggg ccugaacagc gugcccaagc ugaaagugug gacaaucagc 1200

augcgccaga acuacugggg cagcgagggc agacuucugc ugcugggaaa caagaucuac 1260

aucuacaccc gguccaccag cuggcacagc aaacugcagc ugggaaucau cgacaucacc 1320

gacuacagcg acauccggau caaguggacc uggcacaacg ugcugagcag acccggcaac 1380

aaugagugcc cuuggggcca cagcugcccc gauggaugua ucaccggcgu guacaccgac 1440

gccuaccccc ugaauccuac cggcuccauc guguccagcg ugauccugga cagccagaaa 1500

agcagaguga accccgugau cacauacagc accgccaccg agagagugaa cgaacuggcc 1560

aucagaaaca agacccugag cgccggcuac accaccacaa gcugcaucac acacuacaac 1620

aagggcuacu gcuuccacau cguggaaauc aaccacaagu cccugaacac cuuccagccc 1680

augcuguuca agaccgagau ccccaagagc ugcucc 1716

<210> SEQ ID NO 64
<211> LENGTH: 1617

-continued

<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 64

augcccauca gcauccugcu gaucaucacc acaaugauca uggccagcca cugccagauc 60

gacaucacca agcugcagca cgugggcgug cucgugaaca gccccaaggg caugaagauc 120

agccagaacu ucgagacacg cuaccugauc cugagccuga uccccaagau cgaggacagc 180

aacagcugcg gcgaccagca gaucaagcag uacaagcggc ugcuggacag acugaucauc 240

ccccuguacg acggccugcg gcugcagaaa gacgugaucg ugaccaacca ggaaagcaac 300

gagaacaccg acccccggac cgagagauuc uucggcggcg ugaucggcac aaucgcccug 360

ggaguggcca caagcgccca gauuacagcc gcuguggccc ugguggaagc caagcaggcc 420

agaagcgaca ucgagaagcu gaaagaggcc auccgggaca ccaacaaggc cgugcagagc 480

gugcagucca gcgugggcaa ucugaucgug gccaucaagu ccgugcagga cuacgugaac 540

aaagaaaucg ugcccucuau cgcccggcug ggcugugaag cugccggacu gcagcugggc 600

auugcccuga cacagcacua cagcgagcug accaacaucu ucggcgacaa caucggcagc 660

cugcaggaaa agggcauuaa gcugcaggga aucgccagcc uguaccgcac caacaucacc 720

gagaucuuca ccaccagcac cguggauaag uacgacaucu acgaccugcu guucaccgag 780

agcaucaaag ugcgcgugau cgacguggac cugaacgacu acagcaucac ccugcaagug 840

cggcugcccc ugcugaccag acugcugaac acccagaucu acaaggugga cagcaucucc 900

uacaacaucc agaaccgcga gugguacauc ccucugccca gccacauuau gaccaagggc 960

gccuuucugg gcggagccga cgugaaagag ugcaucgagg ccuucagcag cuacaucugc 1020

cccagcgacc cuggcuucgu gcugaaccac gagauggaaa gcugccugag cggcaacauc 1080

agccagugcc ccagaaccac cgugaccucc gacaucgugc ccagauacgc cuucgugaau 1140

ggcggcgugg uggccaacug caucaccacc accuguaccu gcaacggcau cggcaaccgg 1200

aucaaccagc cucccgauca gggcgugaag auuaucaccc acaaagagug uaacaccauc 1260

ggcaucaacg gcaugcuguu caauaccaac aaagagggca cccuggccuu cuacaccccc 1320

gacgauauca cccugaacaa cuccguggcu cuggacccca ucgacaucuc caucgagcug 1380

aacaaggcca agagcgaccu ggaagagucc aaagagugga uccggcggag caaccagaag 1440

cuggacucua ucggcagcug gcaccagagc agcaccacca ucaucgugau ccugauuaug 1500

augauuaucc uguucaucau caacauuacc aucaucacua ucgccauuaa guacuaccgg 1560

auccagaaac ggaaccgggu ggaccagaau gacaagcccu acgugcugac aaacaag 1617

<210> SEQ ID NO 65
<211> LENGTH: 4062
<212> TYPE: RNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Middle East respiratory syndrome coronavirus

<400> SEQUENCE: 65

augauacacu caguguuucu acugauguuc uuguuaacac cuacagaaag uuacguugau 60

guagggccag auucuguuaa gucugcuugu auugagguug auauacaaca gaccuucuuu 120

gauaaaacuu ggccuaggcc aauugauguu ucuaaggcug acgguauuau auacccucaa 180

ggccguacau auucuaacau aacuaucacu uaucaagguc uuuuucccua ucagggagac 240

-continued

cauggugaua uguauguuua cucugcagga caugcuacag gcacaacucc acaaaaguug 300

uuuguagcua acuauucuca ggacgucaaa caguuugcua auggguuugu cguccguaua 360

ggagcagcug ccaauuccac uggcacuguu auuauuagcc caucuaccag cgcuacuaua 420

cgaaaaauuu acccugcuuu uaugcugggu ucuucaguug guaauuucuc agaugguaaa 480

augggccgcu ucuucaauca uacucuaguu cuuuugcccg auggaugugg cacuuuacuu 540

agagcuuuuu auuguauucu agagccucgc ucuggaaauc auuguccugc uggcaauucc 600

uauacuucuu uugccacuua ucacacuccu gcaacagauu guucugaugg caauuacaau 660

cguaaugcca gucugaacuc uuuuaaggag uauuuuaauu uacguaacug caccuuuaug 720

uacacuuaua acauuaccga agaugagauu uuagaguggu uuggcauuac acaaacugcu 780

caagguguuc accucuucuc aucucgguau guugauuugu acggcggcaa uauguuucaa 840

uuugccaccu ugccuguuua ugauacuauu aaguauuauu cuaucauucc ucacaguauu 900

cguucuaucc aaagugauag aaaagcuugg gcugccuucu acguauauaa acuucaaccg 960

uuaacuuucc uguuggauuu uucuguugau gguuauauac gcagagcuau agacuguggu 1020

uuuaaugauu ugucacaacu ccacugcuca uaugaauccu ucgauguuga aucuggaguu 1080

uauucaguuu cgucuuucga agcaaaaccu ucuggcucag uuguggaaca ggcugaaggu 1140

guugaaugug auuuuucacc ucuucugucu ggcacaccuc cucagguuua uaauuucaag 1200

cguuugguuu uuaccaauug caauuauaau cuuaccaaau ugcuuucacu uuuuucugug 1260

aaugauuuua cuuguaguca aauaucucca gcagcaauug cuagcaacug uuauucuuca 1320

cugauuuugg auuauuuuuc auacccacuu aguaugaaau ccgaucucag uguuaguucu 1380

gcugguccaa uaucccaguu uaauuauaaa caguccuuuu cuaaucccac auguuugauc 1440

uuagcgacug uuccucauaa ccuuacuacu auuacuaagc cucuuaagua cagcuauauu 1500

aacaagugcu cucgucuucu uucugaugau cguacugaag uaccucaguu agugaacgcu 1560

aaucaauacu cacccugugu auccauuguc ccauccacug ugugggaaga cggugauuau 1620

uauaggaaac aacuaucucc acuugaaggu gguggcuggc uuguugcuag uggcucaacu 1680

guugccauga cugagcaauu acagaugggc uuugguauua caguucaaua ugguacagac 1740

accaauagug uuugccccaa gcuugaauuu gcuaaugaca caaaaauugc cucucaauua 1800

ggcaauugcg uggaauauuc ccucuauggu guuucgggcc gugguguuuu ucagaauugc 1860

acagcuguag guguucgaca gcagcgcuuu guuuaugaug cguaccagaa uuuaguuggc 1920

uauuauucug augauggcaa cuacuacugu cugcgugcuu guguuagugu uccuguuucu 1980

gucaucuaug auaaagaaac uaaaacccac gcuacucuau uugguagugu ugcaugugaa 2040

cacauuucuu cuaccauguc ucaauacucc cguucuacgc gaucaaugcu uaaacggcga 2100

gauucuacau auggcccccu ucagacaccu guugguugug uccuaggacu uguuaauucc 2160

ucuuuguucg uagaggacug caaguugccu cucggucaau cucucugugc ucuuccugac 2220

acaccuagua cucucacacc ucgcagugug cgcucugugc caggugaaau gcgcuuggca 2280

uccauugcuu uuaaucaucc cauucagguu gaucaacuua auaguaguua uuuuaaauua 2340

aguauaccca cuaauuuuuc cuuuggugug acucaggagu acauucagac aaccauucag 2400

aaaguuacug uugauuguaa acaguacguu ugcaaugguu uccagaagug ugagcaauua 2460

cugcgcgagu auggccaguu uuguuccaaa auaaaccagg cucuccaugg ugccaauuua 2520

cgccaggaug auucuguacg uaauuuguuu gcgagcguga aaagcucuca aucaucuccu 2580

aucauaccag guuuuggagg ugacuuuaau uugacacuuc uagaaccugu uucuauaucu 2640

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acuggcaguc guagugcacg uagugcuauu gaggauuugc uauuugacaa agucacuaua 2700

gcugauccug guuauaugca agguuacgau gauuguaugc agcaaggucc agcaucagcu 2760

cgugaucuua uuugugcuca auauguggcu gguuauaaag uauuaccucc ucuuauggau 2820

guuaauaugg aagccgcgua uacuucaucu uugcuuggca gcauagcagg uguuggcugg 2880

acugcuggcu uauccuccuu ugcugcuauu ccauuugcac agaguauyuu uuauagguua 2940

aacgguguug gcauuacuca acagguucuu ucagagaacc aaaagcuuau ugccaauaag 3000

uuuaaucagg cucugggagc uaugcaaaca ggcuucacua caacuaauga agcuuuucgg 3060

aagguucagg augcugugaa caacaaugca caggcucuau ccaaauuagc uagcgagcua 3120

ucuaauacuu uuggugcuau uuccgccucu auuggagaca ucauacaacg ucuugauguu 3180

cucgaacagg acgcccaaau agacagacuu auuaauggcc guuugacaac acuaaaugcu 3240

uuuguugcac agcagcuugu ucguuccgaa ucagcugcuc uuuccgcuca auuggcuaaa 3300

gauaaaguca augagugugu caaggcacaa uccaagcguu cuggauuuug cggucaaggc 3360

acacauauag uguccuuugu uguaaaugcc ccuaauggcc uuuacuuuau gcauguuggu 3420

uauuacccua gcaaccacau ugagguuguu ucugcuuaug gucuuugcga ugcagcuaac 3480

ccuacuaauu guauagcccc uguuaauggc uacuuuauua aaacuaauaa cacuaggauu 3540

guugaugagu ggucauauac uggcucgucc uucuaugcac cugagcccau caccucucuu 3600

aauacuaagu auguugcacc acaggugaca uaccaaaaca uuucuacuaa ccucccuccu 3660

ccucuucucg gcaauuccac cgggauugac uuccaagaug aguuggauga guuuuucaaa 3720

aauguuagca ccaguauacc uaauuuuggu ucucuaacac agauuaauac uacauuacuc 3780

gaucuuaccu acgagauguu gucucuucaa caaguuguua aagcccuuaa ugagucuuac 3840

auagaccuua aagagcuugg caauuauacu uauuacaaca aauggccgug guacauuugg 3900

cuugguuuca uugcugggcu uguugccuua gcucuaugcg ucuucuucau acugugcugc 3960

acugguugug gcacaaacug uaugggaaaa cuuaagugua aucguuguug ugauagauac 4020

gaggaauacg accucgagcc gcauaagguu cauguucacu aa 4062

<210> SEQ ID NO 66
<211> LENGTH: 4062
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 66

augauacacu caguguuucu acugauguuc uuguuaacac cuacagaaag uuacguugau 60

guagggccag auucuguuaa gucugcuugu auugagguug auauacaaca gacuuucuuu 120

gauaaaacuu ggccuaggcc aauugauguu ucuaaggcug acgguauuau auacccucaa 180

ggccguacau auucuaacau aacuaucacu uaucaagguc uuuuucccua ucagggagac 240

cauggugaua uguauguuua cucugcagga caugcuacag gcacaacucc acaaaaguug 300

uuuguagcua acuauucuca ggacgucaaa caguuugcua auggguuugu cguccguaua 360

ggagcagcug ccaauuccac uggcacuguu auuauuagcc caucuaccag cgcuacuaua 420

cgaaaaauuu acccugcuuu uaugcugggu ucuucaguug guaauuucuc agaugguaaa 480

augggccgcu ucuucaauca uacucuaguu cuuuugcccg auggaugugg cacuuuacuu 540

agagcuuuuu auuguauucu ggagccucgc ucuggaaauc auuguccugc uggcaauucc 600

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uauacuucuu uugccacuua ucacacuccu gcaacagauu guucugaugg caauuacaau 660

cguaaugcca gucugaacuc uuuuaaggag uauuuuaauu uacguaacug caccuuuaug 720

uacacuuaua acauuaccga agaugagauu uuagaguggu uuggcauuac acaaacugcu 780

caagguguuc accucuucuc aucucgguau guugauuugu acggcggcaa uauguuucaa 840

uuugccaccu ugccuguuua ugauacuauu aaguauuauu cuaucauucc ucacaguauu 900

cguucuaucc aaagugauag aaaagcuugg gcugccuucu acguauauaa acuucaaccg 960

uuaacuuucc uguuggauuu uucuguugau gguuauauac gcagagcuau agacuguggu 1020

uuuaaugauu ugucacaacu ccacugcuca uaugaauccu ucgauguuga aucuggaguu 1080

uauucaguuu cgucuuucga agcaaaaccu ucuggcucag uuguggaaca ggcugaaggu 1140

guugaaugug auuuuucacc ucuucugucu ggcacaccuc cucagguuua uaauuucaag 1200

cguuugguuu uuaccaauug caauuauaau cuuaccaaau ugcuuucacu uuuuucugug 1260

aaugauuuua cuuguaguca aauaucucca gcagcaauug cuagcaacug uuauucuuca 1320

cugauuuugg auuacuuuuc auacccacuu aguaugaaau ccgaucucag uguuaguucu 1380

gcugguccaa uaucccaguu uaauuauaaa caguccuuuu cuaaucccac auguuugauu 1440

uuagcgacug uuccucauaa ccuuacuacu auuacuaagc cucuuaagua cagcuauauu 1500

aacaagugcu cucgucuucu uucugaugau cguacugaag uaccucaguu agugaacgcu 1560

aaucaauacu cacccugugu auccauuguc ccauccacug ugugggaaga cggugauuau 1620

uauaggaaac aacuaucucc acuugaaggu gguggcuggc uuguugcuag uggcucaacu 1680

guugccauga cugagcaauu acagaugggc uuugguauua caguucaaua ugguacagac 1740

accaauagug uuugccccaa gcuugaauuu gcuaaugaca caaaaauugc cucucaauua 1800

ggcaauugcg uggaauauuc ccucuauggu guuucgggcc gugguguuuu ucagaauugc 1860

acagcuguag guguucgaca gcagcgcuuu guuuaugaug cguaccagaa uuuaguuggc 1920

uauuauucug augauggcaa cuacuacugu uugcgugcuu guguuagugu uccuguuucu 1980

gucaucuaug auaaagaaac uaaaacccac gcuacucuau uugguagugu ugcaugugaa 2040

cacauuucuu cuaccauguc ucaauacucc cguucuacgc gaucaaugcu uaaacggcga 2100

gauucuacau auggcccccu ucagacaccu guugguugug uccuaggacu uguuaauucc 2160

ucuuuguucg uagaggacug caaguugccu cuuggucaau cucucugugc ucuuccugac 2220

acaccuagua cucucacacc ucgcagugug cgcucuguuc caggugaaau gcgcuuggca 2280

uccauugcuu uuaaucaucc uauucagguu gaucaacuua auaguaguua uuuuaaauua 2340

aguauaccca cuaauuuuuc cuuuggugug acucaggagu acauucagac aaccauucag 2400

aaaguuacug uugauuguaa acaguacguu ugcaaugguu uccagaagug ugagcaauua 2460

cugcgcgagu auggccaguu uuguuccaaa auaaaccagg cucuccaugg ugccaauuua 2520

cgccaggaug auucuguacg uaauuuguuu gcgagcguga aaagcucuca aucaucuccu 2580

aucauaccag guuuuggagg ugacuuuaau uugacacuuc uggaaccugu uucuauaucu 2640

acuggcaguc guagugcacg uagugcuauu gaggauuugc uauuugacaa agucacuaua 2700

gcugauccug guuauaugca agguuacgau gauugcaugc agcaaggucc agcaucagcu 2760

cgugaucuua uuugugcuca auauguggcu gguuacaaag uauuaccucc ucuuauggau 2820

guuaauaugg aagccgcgua uacuucaucu uugcuuggca gcauagcagg uguuggcugg 2880

acugcuggcu uauccuccuu ugcugcuauu ccauuugcac agaguaucuu uuauagguua 2940

aacgguguug gcauuacuca acagguucuu ucagagaacc aaaagcuuau ugccaauaag 3000

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uuuaaucagg cucugggagc uaugcaaaca ggcuucacua caacuaauga agcuuuucag 3060

aagguucagg augcugugaa caacaaugca caggcucuau ccaaauuagc uagcgagcua 3120

ucuaauacuu uuggugcuau uuccgccucu auuggagaca ucauacaacg ucuugauguu 3180

cucgaacagg acgcccaaau agacagacuu auuaauggcc guuugacaac acuaaaugcu 3240

uuuguugcac agcagcuugu ucguuccgaa ucagcugcuc uuuccgcuca auuggcuaaa 3300

gauaaaguca augagugugu caaggcacaa uccaagcguu cuggauuuug cggucaaggc 3360

acacauauag uguccuuugu uguaaaugcc ccuaauggcc uuuacuucau gcauguuggu 3420

uauuacccua gcaaccacau ugagguuguu ucugcuuaug gucuuugcga ugcagcuaac 3480

ccuacuaauu guauagcccc uguuaauggc uacuuuauua aaacuaauaa cacuaggauu 3540

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aauacuaagu auguugcacc acaggugaca uaccaaaaca uuucuacuaa ccucccuccu 3660

ccucuucucg gcaauuccac cgggauugac uuccaagaug aguuggauga guuuuucaaa 3720

aauguuagca ccaguauacc uaauuuuggu ucccuaacac agauuaauac uacauuacuc 3780

gaucuuaccu acgagauguu gucucuucaa caaguuguua aagcccuuaa ugagucuuac 3840

auagaccuua aagagcuugg caauuauacu uauuacaaca aauggccgug guacauuugg 3900

cuugguuuca uugcugggcu uguugccuua gcucuaugcg ucuucuucau acugugcugc 3960

acugguugug gcacaaacug uaugggaaaa cuuaagugua aucguuguug ugauagauac 4020

gaggaauacg accucgagcc gcauaagguu cauguucacu aa 4062

<210> SEQ ID NO 67
<211> LENGTH: 1845
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 67

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cucccgcugg gacagucccu gugugcgcug ccugacacuc cuagcacucu gaccccacgc 120

uccgugcggu cggugccugg cgaaaugcgg cuggccucca ucgccuucaa ucacccaauc 180

caaguggauc agcugaauag cucguauuuc aagcugucca ucccccacgaa cuucucguuc 240

ggggucaccc aggaguacau ccagaccaca auucagaagg ucaccgucga uugcaagcaa 300

uacgugugca acggcuucca gaagugcgag cagcugcuga gagaauacgg gcaguuuugc 360

agcaagauca accaggcgcu gcauggagcu aacuugcgcc aggacgacuc cgugcgcaac 420

cucuuugccu cugugaaguc aucccagucc uccccaauca ucccgggauu cggaggggac 480

uucaaccuga cccuccugga gcccgugucg aucagcaccg guagcagauc ggcgcgcuca 540

gccauugaag aucuucuguu cgacaagguc accaucgccg auccgggcua caugcaggga 600

uacgacgacu guaugcagca gggaccagcc uccgcgaggg accucaucug cgcgcaauac 660

guggccgggu acaaagugcu gccuccucug auggauguga acauggaggc cgcuuauacu 720

ucgucccugc ucggcucuau cgccggcgug ggguggaccg ccggccuguc cuccuucgcc 780

gcuauccccu uugcacaauc cauuuucuac cggcucaacg gcgugggcau uacucaacaa 840

guccugucgg agaaccagaa guugaucgca aacaaguuca aucaggcccu gggggccaug 900

cagacuggau ucacuacgac uaacgaagcg uuccagaagg uccaggacgc ugugaacaac 960

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aacgcccagg cgcucucaaa gcuggccucc gaacucagca acaccuucgg agccaucagc 1020

gcaucgaucg gugacauaau ucagcggcug gacgugcugg agcaggacgc ccagaucgac 1080

cgccucauca acggacggcu gaccaccuug aaugccuucg uggcacaaca gcugguccgg 1140

agcgaaucag cggcacuuuc cgcccaacuc gccaaggaca aagucaacga augcgugaag 1200

gcccagucca agaggcccgg uuucugcggu caaggaaccc auauuguguc cuucgucgug 1260

aacgcgccca acggucugua cuuuaugcac gucggcuacu acccgagcaa ucauaucgaa 1320

gugguguccg ccuacggccu gugcgaugcc gcuaacccca cuaacuguau ugccccugug 1380

aacggauauu uuauuaagac caacaacacc cgcauugugg acgaaugguc auacaccggu 1440

ucguccuucu acgcgcccga gcccaucacu ucacugaaca ccaaauacgu ggcuccgcaa 1500

gugaccuacc agaacaucuc caccaauuug ccgccgccgc ugcucggaaa cagcaccgga 1560

auugauuucc aagaugaacu ggacgaauuc uucaagaacg uguccacuuc cauucccaac 1620

uucggaagcc ugacacagau caacaccacc cuucucgacc ugaccuacga gaugcugagc 1680

cuucaacaag uggucaaggc ccugaacgag agcuacaucg accugaagga gcugggcaac 1740

uauaccuacu acaacaagug gccggacaag auugaggaga uucugucgaa aaucuaccac 1800

auugaaaacg agaucgccag aaucaagaag cuuaucggcg aagcc 1845

<210> SEQ ID NO 68
<211> LENGTH: 4071
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 68

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agcuaugugg acgugggccc cgauagcgug aaguccgccu guaucgaagu ggacauccag 120

cagaccuuuu ucgacaagac cuggcccaga cccaucgacg uguccaaggc cgacggcauc 180

aucuauccac aaggccggac cuacagcaac aucaccauua ccuaccaggg ccuguuccca 240

uaucaaggcg accacggcga uauguacgug uacucugccg gccacgccac cggcaccaca 300

ccccagaaac uguucguggc caacuacagc caggacguga agcaguucgc caacggcuuc 360

gucgugcgga uuggcgccgc ugccaauagc accggcacag ugaucaucag ccccagcacc 420

agcgccacca uccggaagau cuaccccgcc uucaugcugg gcagcuccgu gggcaauuuc 480

agcgacggca agaugggccg guucuucaac cacacccugg ugcugcugcc cgauggcugu 540

ggcacacugc ugagagccuu cuacugcauc cuggaaccca gaagcggcaa ccacugcccu 600

gccggcaaua gcuacaccag cuucgccacc uaccacacac ccgccaccga uugcuccgac 660

ggcaacuaca accggaacgc cagccugaac agcuucaaag aguacuucaa ccugcggaac 720

ugcaccuuca uguacaccua caauaucacc gaggacgaga uccuggaaug guucggcauc 780

acccagaccg cccagggcgu gcaccuguuc agcagcagau acguggaccu guacggcggc 840

aacauguucc aguuugccac ccugcccgug uacgacacca ucaaguacua cagcaucauc 900

ccccacagca uccgguccau ccagagcgac agaaaagccu gggccgccuu cuacguguac 960

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aucgacugcg gcuucaacga ccugagccag cugcacugcu ccuacgagag cuucgacgug 1080

gaaagcggcg uguacagcgu guccagcuuc gaggccaagc cuagcggcag cgugguggaa 1140

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agcguguccu ccgccggacc caucagccag uucaacuaca agcagagcuu cagcaacccu 1440

accugccuga uucuggccac cgugccccac aaucugacca ccaucaccaa gccccugaag 1500

uacagcuaca ucaacaagug cagcagacug cuguccgacg accggaccga agugccccag 1560

cucgugaacg ccaaccagua cagccccugc guguccaucg ugcccagcac cgugugggag 1620

gacggcgacu acuacagaaa gcagcugagc ccccuggaag gcggcggaug gcugguggcu 1680

ucuggaagca caguggccau gaccgagcag cugcagaugg gcuuuggcau caccgugcag 1740

uacggcaccg acaccaacag cgugugcccc aagcuggaau ucgccaauga caccaagauc 1800

gccagccagc ugggaaacug cguggaauac ucccuguaug gcguguccgg acggggcgug 1860

uuccagaauu gcacagcagu gggagugcgg cagcagagau ucguguacga ugccuaccag 1920

aaccucgugg gcuacuacag cgacgacggc aauuacuacu gccugcgggc cugugugucc 1980

gugcccgugu ccgugaucua cgacaaagag acaaagaccc acgccacacu guucggcucc 2040

guggccugcg agcacaucag cuccaccaug agccaguacu cccgcuccac ccgguccaug 2100

cugaagcgga gagauagcac cuacggcccc cugcagacac cugugggaug ugugcugggc 2160

cucgugaaca gcucccuguu uguggaagau ugcaagcugc cccugggcca gagccugugu 2220

gcccugccag auacccccuag cacccugacc ccuagaagcg ugcgcucugu gcccggcgaa 2280

augcggcugg ccucuaucgc cuucaaucac cccauccagg uggaccagcu gaacuccagc 2340

uacuucaagc ugagcauccc caccaacuuc agcuucggcg ugacccagga guacauccag 2400

accacaaucc agaaagugac cguggacugc aagcaguacg ugugcaacgg cuuucagaag 2460

ugcgaacagc ugcugcgcga guacggccag uucugcagca agaucaacca ggcccugcac 2520

ggcgccaacc ugagacagga ugacagcgug cggaaccugu ucgccagcgu gaaaagcagc 2580

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ccccugaugg acgugaacau ggaagccgcc uacaccucca gccugcuggg cucuauugcu 2880

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aucgccaaca aguuuaacca ggcacugggc gccaugcaga ccggcuucac caccaccaac 3060

gaggccuuca gaaaggugca ggacgccgug aacaacaacg cccaggcucu gagcaagcug 3120

gccuccgagc ugagcaauac cuucggcgcc aucagcgccu ccaucggcga caucauccag 3180

cggcuggacg ugcuggaaca ggacgcccag aucgaccggc ugaucaacgg cagacugacc 3240

acccugaacg ccuucguggc acagcagcuc gugcggagcg aaucugccgc ucugucugcu 3300

cagcuggcca aggacaaagu gaacgagugc gugaaggccc aguccaagcg gagcggcuuu 3360

uguggccagg gcacccacau cguguccuuc gucgugaaug cccccaacgg ccuguacuuu 3420

augcacgugg gcuauuaccc cagcaaccac aucgaggugg uguccgccua uggccugugc 3480

gacgccgcca auccuaccaa cuguaucgcc cccgugaacg gcuacuucau caagaccaac 3540

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aacacccgga ucguggacga gugguccuac acaggcagca gcuucuacgc ccccgagccc 3600

aucaccuccc ugaacaccaa auacguggcc ccccaaguga cauaccagaa caucuccacc 3660

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gaguucuuca agaacguguc caccuccauc cccaacuucg gcagccugac ccagaucaac 3780

accacucugc uggaccugac cuacgagaug cugucccugc aacaggucgu gaaagcccug 3840

aacgagagcu acaucgaccu gaaagagcug gggaacuaca ccuacuacaa caaguggccu 3900

ugguacauuu ggcugggcuu uaucgccggc cugguggccc uggcccugug cguguucuuc 3960

auccugugcu gcaccggcug cggcaccaau ugcaugggca agcugaaaug caaccggugc 4020

ugcgacagau acgaggaaua cgaccuggaa ccucacaaag ugcaugugca c 4071

<210> SEQ ID NO 69
<211> LENGTH: 1864
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 69

ucaagcuuuu ggacccucgu acagaagcua auacgacuca cuauagggaa auaagagaga 60

aaagaagagu aagaagaaau auaagagcca ccaugggucu caaggugaac gucucugccg 120

uauucauggc aguacuguua acucuccaaa cacccgccgg ucaaauucau uggggcaauc 180

ucucuaagau agggguagua ggaauaggaa gugcaagcua caaaguuaug acucguucca 240

gccaucaauc auuagucaua aaauuaaugc ccaauauaac ucuccucaau aacugcacga 300

ggguagagau ugcagaauac aggagacuac uaagaacagu uuuggaacca auuagggaug 360

cacuuaaugc aaugacccag aacauaaggc cgguucagag cguagcuuca aguaggagac 420

acaagagauu ugcgggagua guccuggcag gugcggcccu agguguugcc acagcugcuc 480

agauaacagc cggcauugca cuucaccggu ccaugcugaa cucucaggcc aucgacaauc 540

ugagagcgag ccuggaaacu acuaaucagg caauugaggc aaucagacaa gcagggcagg 600

agaugauauu ggcuguucag gguguccaag acuacaucaa uaaugagcug auaccgucua 660

ugaaccagcu aucuugugau cuaaucgguc agaagcucgg gcucaaauug cuuagauacu 720

auacagaaau ccugucauua uuuggcccca gccuacggga ccccauaucu gcggagauau 780

cuauccaggc uuugaguuau gcacuuggag gagauaucaa uaagguguua gaaaagcucg 840

gauacagugg aggcgauuua cuaggcaucu uagagagcag aggaauaaag gcucggauaa 900

cucacgucga cacagagucc uacuucauag uccucaguau agccuauccg acgcuguccg 960

agauuaaggg ggugauuguc caccggcuag agggggucuc guacaacaua ggcucucaag 1020

agugguauac cacugugccc aaguauguug caacccaagg guaccuuauc ucgaauuuug 1080

augagucauc auguacuuuc augccagagg ggacugugug cagccaaaau gccuuguacc 1140

cgaugagucc ucugcuccaa gaaugccucc ggggguccac caaguccugu gcucguacac 1200

ucguauccgg gucuuuuggg aaccgguuca uuuuaucaca agggaaccua auagccaauu 1260

gugcaucaau ucuuuguaag uguuacacaa cagguacgau uauuaaucaa gacccugaca 1320

agauccuaac auacauugcu gccgaucgcu gcccgguagu cgaggugaac ggcgugacca 1380

uccaagucgg gagcaggagg uauccagacg cuguguacuu gcacagaauu gaccucgguc 1440

cucccauauc auuggagagg uuggacguag ggacaaaucu ggggaaugca auugccaaau 1500

uggaggaugc caaggaauug uuggaaucau cggaccagau auugagaagu augaaagguu 1560

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uaucgagcac uagcauaguc uacauccuga uugcagugug ucuuggaggg uugauaggga 1620

uccccacuuu aauauguugc ugcaggggge guuguaacaa aaagggagaa caaguuggua 1680

ugucaagacc aggccuaaag ccugaccuua caggaacauc aaaauccuau guaagaucgc 1740

uuugaugaua auaggcugga gccucggugg ccaagcuucu ugccccuugg gccucccccc 1800

agccccuccu ccccuuccug cacccguacc cccguggucu uugaauaaag ucugaguggg 1860

cggc 1864

<210> SEQ ID NO 70
<211> LENGTH: 1653
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 70

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cccgccgguc aaauucauug gggcaaucuc ucuaagauag ggguaguagg aauaggaagu 120

gcaagcuaca aaguuaugac ucguuccagc caucaaucau uagucauaaa auuaaugccc 180

aauauaacuc uccucaauaa cugcacgagg guagagauug cagaauacag gagacuacua 240

agaacaguuu uggaaccaau uagggaugca cuuaaugcaa ugacccagaa cauaaggccg 300

guucagagcg uagcuucaag uaggagacac aagagauuug cgggaguagu ccuggcaggu 360

gcggcccuag guguugccac agcugcucag auaacagccg gcauugcacu ucaccggucc 420

augcugaacu cucaggccau cgacaaucug agagcgagcc uggaaacuac uaaucaggca 480

auugaggcaa ucagacaagc agggcaggag augauauugg cuguucaggg uguccaagac 540

uacaucaaua augagcugau accgucuaug aaccagcuau cuugugaucu aaucggucag 600

aagcucgggc ucaaauugcu uagauacuau acagaaaucc ugucauuauu uggccccagc 660

cuacgggacc ccauaucugc ggagauaucu auccaggcuu ugaguuaugc acuuggagga 720

gauaucaaua agguguuaga aaagcucgga uacaguggag gcgauuuacu aggcaucuua 780

gagagcagag gaauaaaggc ucggauaacu cacgucgaca cagaguccua cuucauaguc 840

cucaguauag ccuauccgac gcuguccgag auuaaggggg ugauugucca ccggcuagag 900

ggggucucgu acaacauagg cucucaagag ugguauacca cugugcccaa guauguugca 960

acccaagggu accuuaucuc gaauuuugau gagucaucau guacuuucau gccagagggg 1020

acugugugca gccaaaaugc cuuguacccg augaguccuc ugcuccaaga augccuccgg 1080

ggguccacca aguccugugc ucguacacuc guauccgggu cuuuugggaa ccgguucauu 1140

uuaucacaag ggaaccuaau agccaauugu gcaucaauuc uuuguaagug uuacacaaca 1200

gguacgauua uuaaucaaga cccugacaag auccuaacau acauugcugc cgaucgcugc 1260

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gaccagauau ugagaaguau gaaagguuua ucgagcacua gcauagucua cauccugauu 1500

gcaguguguc uuggaggguu gauagggauc cccacuuuaa uauguugcug caggggggcgu 1560

uguaacaaaa agggagaaca aguugguaug ucaagaccag gccuaaagcc ugaccuuaca 1620

ggaacaucaa aauccuaugu aagaucgcuu uga 1653

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<210> SEQ ID NO 71
<211> LENGTH: 1925
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 71

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gugaacgucu cugccguauu cauggcagua cuguuaacuc uccaaacacc cgccggucaa 120

auucauuggg gcaaucucuc uaagauaggg guaguaggaa uaggaagugc aagcuacaaa 180

guuaugacuc guuccagcca ucaaucauua gucauaaaau uaaugcccaa uauaacucuc 240

cucaauaacu gcacgagggu agagauugca gaauacagga gacuacuaag aacaguuuug 300

gaaccaauua gggaugcacu uaaugcaaug acccagaaca uaaggccggu ucagagcgua 360

gcuucaagua ggagacacaa gagauuugcg ggaguagucc uggcaggugc ggcccuaggu 420

guugccacag cugcucagau aacagccggc auugcacuuc accgguccau gcugaacucu 480

caggccaucg acaaucugag agcgagccug gaaacuacua aucaggcaau ugaggcaauc 540

agacaagcag ggcaggagau gauauuggcu guucagggug uccaagacua caucaauaau 600

gagcugauac cgucuaugaa ccagcuaucu ugugaucuaa ucggucagaa gcucgggcuc 660

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uauccgacgc uguccgagau uaaggggugg auuguccacc ggcuagaggg ggucucguac 960

aacauaggcu cucaagagug guauaccacu gugcccaagu auguugcaac ccaaggguac 1020

cuuaucucga auuuugauga gucaucaugu acuuucaugc cagaggggac ugugugcagc 1080

caaaaugccu uguacccgau gaguccucug cuccaagaau gccuccgggg guccaccaag 1140

uccugugcuc guacacucgu auccgggucu uuugggaacc gguucauuuu aucacaaggg 1200

aaccuaauag ccaauugugc aucaauucuu uguaaguguu acacaacagg uacgauuauu 1260

aaucaagacc cugacaagau ccuaacauac auugcugccg aucgcugccc gguagucgag 1320

gugaacggcg ugaccaucca agucgggagc aggagguauc cagacgcugu guacuugcac 1380

agaauugacc ucgguccucc cauaucauug gagagguugg acguagggac aaaucugggg 1440

aaugcaauug ccaaauugga ggaugccaag gaauuguugg aaucaucgga ccagauauug 1500

agaaguauga aagguuuauc gagcacuagc auagucuaca uccugauugc agugugucuu 1560

ggaggguuga uagggauccc cacuuuaaua uguugcugca gggggcguug uaacaaaaag 1620

ggagaacaag uugguauguc aagaccaggc cuaaagccug accuuacagg aacaucaaaa 1680

uccuauguaa gaucgcuuug augauaauag gcuggagccu cgguggccaa gcuucuugcc 1740

ccuugggccu ccccccagcc ccuccucccc uuccugcacc cguacccccg uggucuuuga 1800

auaaagucug agugggcggc aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1860

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1920

ucuag 1925

<210> SEQ ID NO 72
<211> LENGTH: 1864

-continued

<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 72

ucaagcuuuu ggacccucgu acagaagcua auacgacuca cuauagggaa auaagagaga 60

aaagaagagu aagaagaaau auaagagcca ccaugggucu caaggugaac gucucuguca 120

uauucauggc aguacuguua acucuucaaa cacccaccgg ucaaauccau uggggcaauc 180

ucucuaagau agggguggua gggguaggaa gugcaagcua caaaguuaug acucguucca 240

gccaucaauc auuagucaua aaguuaaugc ccaauauaac ucuccucaac aauugcacga 300

ggguagggau ugcagaauac aggagacuac ugagaacagu ucuggaacca auuagagaug 360

cacuuaaugc aaugacccag aauauaagac cgguucagag uguagcuuca aguaggagac 420

acaagagauu ugcgggaguu guccuggcag gugcggcccu aggcguugcc acagcugcuc 480

aaauaacagc cgguauugca cuucaccagu ccaugcugaa cucucaagcc aucgacaauc 540

ugagagcgag ccuagaaacu acuaaucagg caauugaggc aaucagacaa gcagggcagg 600

agaugauauu ggcuguucag gguguccaag acuacaucaa uaaugagcug auaccgucua 660

ugaaucaacu aucuugugau uuaaucggcc agaagcuagg gcucaaauug cucagauacu 720

auacagaaau ccugucauua uuuggcccca gcuuacggga ccccauaucu gcggagauau 780

cuauccaggc uuugagcuau gcgcuuggag gagauaucaa uaagguguug gaaaagcucg 840

gauacagugg aggugaucua cugggcaucu uagagagcag aggaauaaag gcccggauaa 900

cucacgucga cacagagucc uacuucauug uacucaguau agccuauccg acgcuauccg 960

agauuaaggg ggugauuguc caccggcuag agggggucuc guacaacaua ggcucucaag 1020

agugguauac cacugugccc aaguauguug caacccaagg guaccuuauc ucgaauuuug 1080

augagucauc augcacuuuc augccagagg ggacugugug cagccagaau gccuuguacc 1140

cgaugagucc ucugcuccaa gaaugccucc ggggguccac uaaguccugu gcucguacac 1200

ucguauccgg gucuuucggg aaccgguuca uuuuaucaca ggggaaccua auagccaauu 1260

gugcaucaau ccuuugcaag uguuacacaa caggaacaau cauuaaucaa gacccugaca 1320

agauccuaac auacauugcu gccgaucacu gcccgguggu cgaggugaau ggcgugacca 1380

uccaagucgg gagcaggagg uauccggacg cuguguacuu gcacaggauu gaccucgguc 1440

cucccauauc uuuggagagg uuggacguag ggacaaaucu ggggaaugca auugcuaagu 1500

uggaggaugc caaggaauug uuggagucau cggaccagau auugaggagu augaaagguu 1560

uaucgagcac uaguauaguu uacauccuga uugcagugug ucuuggagga uugauaggga 1620

uccccgcuuu aauauguugc ugcagggggc guuguaacaa gaagggagaa caaguuggua 1680

ugucaagacc aggccuaaag ccugaucuua caggaacauc aaaauccuau guaaggucac 1740

ucugaugaua auaggcugga gccucggugg ccaagcuucu ugccccuugg gccucccccc 1800

agccccuccu ccccuuccug cacccguacc cccguggucu uugaauaaag ucugaguggg 1860

cggc 1864

<210> SEQ ID NO 73
<211> LENGTH: 1653
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

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<400> SEQUENCE: 73

augggucuca aggugaacgu cucugucaua uucauggcag uacuguuaac ucuucaaaca 60

cccaccgguc aaauccauug gggcaaucuc ucuaagauag ggguggguagg gguaggaagu 120

gcaagcuaca aaguuaugac ucguuccagc caucaaucau uagucauaaa guuaaugccc 180

aauauaacuc uccucaacaa uugcacgagg guagggauug cagaauacag gagacuacug 240

agaacaguuc uggaaccaau uagagaugca cuuaaugcaa ugacccagaa uauaagaccg 300

guucagagug uagcuucaag uaggagacac aagagauuug cgggaguugu ccuggcaggu 360

gcggcccuag gcguugccac agcugcucaa auaacagccg guauugcacu ucaccagucc 420

augcugaacu cucaagccau cgacaaucug agagcgagcc uagaaacuac uaaucaggca 480

auugaggcaa ucagacaagc agggcaggag augauauugg cuguucaggg uguccaagac 540

uacaucaaua augagcugau accgucuaug aaucaacuau cuugugauuu aaucggccag 600

aagcuagggc ucaaauugcu cagauacuau acagaaaucc ugucauuauu uggccccagc 660

uuacgggacc ccauaucugc ggagauaucu auccaggcuu ugagcuaugc gcuuggagga 720

gauaucaaua agguguugga aaagcucgga uacaguggag gugaucuacu gggcaucuua 780

gagagcagag gaauaaaggc ccggauaacu cacgucgaca cagaguccua cuucauugua 840

cucaguauag ccuauccgac gcuauccgag auuaaggggg ugauugucca ccggcuagag 900

ggggucucgu acaacauagg cucucaagag ugguauacca cugugcccaa guauguugca 960

acccaagggu accuuaucuc gaauuuugau gagucaucau gcacuuucau gccagagggg 1020

acugugugca gccagaaugc cuuguacccg augaguccuc ugcuccaaga augccuccgg 1080

ggguccacua aguccugugc ucguacacuc guauccgggu cuuucgggaa ccgguucauu 1140

uuaucacagg ggaaccuaau agccaauugu gcaucaaucc uuugcaagug uuacacaaca 1200

ggaacaauca uuaaucaaga cccugacaag auccuaacau acauugcugc cgaucacugc 1260

ccgguggucg aggugaaugg cgugaccauc caagucggga gcaggaggua uccggacgcu 1320

guguacuugc acaggauuga ccucgguccu cccauaucuu uggagagguu ggacguaggg 1380

acaaaucugg ggaaugcaau ugcuaaguug gaggaugcca aggaauuguu ggagucaucg 1440

gaccagauau ugaggaguau gaaagguuua ucgagcacua guauaguuua cauccugauu 1500

gcaguguguc uuggaggauu gauagggauc cccgcuuuaa uauguugcug caggggggcgu 1560

uguaacaaga agggagaaca aguugguaug ucaagaccag gccuaaagcc ugaucuuaca 1620

ggaacaucaa aauccuaugu aaggucacuc uga 1653

<210> SEQ ID NO 74
<211> LENGTH: 1925
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 74

ggggaaauaa gagagaaaag aagaguaaga agaaauauaa gagccaccau gggucucaag 60

gugaacgucu cugucauauu cauggcagua cuguuaacuc uucaaacacc caccggucaa 120

auccauuggg gcaaucucuc uaagauaggg gugguagggg uaggaagugc aagcuacaaa 180

guuaugacuc guuccagcca ucaaucauua gucauaaagu uaaugcccaa uauaacucuc 240

cucaacaauu gcacgagggu agggauugca gaauacagga gacuacugag aacaguucug 300

gaaccaauua gagaugcacu uaaugcaaug acccagaaua uaagaccggu ucagagugua 360

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gcuucaagua ggagacacaa gagauuugcg ggaguugucc uggcaggugc ggcccuaggc 420

guugccacag cugcucaaau aacagccggu auugcacuuc accaguccau gcugaacucu 480

caagccaucg acaaucugag agcgagccua gaaacuacua aucaggcaau ugaggcaauc 540

agacaagcag ggcaggagau gauauuggcu guucagggug uccaagacua caucaauaau 600

gagcugauac cgucuaugaa ucaacuaucu ugugauuuaa ucggccagaa gcuagggcuc 660

aaauugcuca gauacuauac agaaauccug ucauuauuug gccccagcuu acgggacccc 720

auaucugcgg agauaucuau ccaggcuuug agcuaugcgc uuggaggaga uaucaauaag 780

guguuggaaa agcucggaua caguggaggu gaucuacugg gcaucuuaga gagcagagga 840

auaaaggccc ggauaacuca cgucgacaca gaguccuacu ucauuguacu caguauagcc 900

uauccgacgc uauccgagau uaaggggugg auuguccacc ggcuagaggg ggucucguac 960

aacauaggcu cucaagagug guauaccacu gugcccaagu auguugcaac ccaaggguac 1020

cuuaucucga auuuugauga gucaucaugc acuuucaugc cagaggggac ugugugcagc 1080

cagaaugccu uguacccgau gaguccucug cuccaagaau gccuccgggg guccacuaag 1140

uccugugcuc guacacucgu auccgggucu uucgggaacc gguucauuuu aucacagggg 1200

aaccuaauag ccaauugugc aucaauccuu ugcaaguguu acacaacagg aacaaucauu 1260

aaucaagacc cugacaagau ccuaacauac auugcugccg aucacugccc gguggucgag 1320

gugaauggcg ugaccaucca agucgggagc aggagguauc cggacgcugu guacuugcac 1380

aggauugacc ucgguccucc cauaucuuug gagagguugg acguagggac aaaucugggg 1440

aaugcaauug cuaaguugga ggaugccaag gaauuguugg agucaucgga ccagauauug 1500

aggaguauga aagguuuauc gagcacuagu auaguuuaca uccugauugc aguguucuu 1560

ggaggauuga uagggauccc cgcuuuaaua uguugcugca gggggcguug uaacaagaag 1620

ggagaacaag uugguauguc aagaccaggc cuaaagccug aucuuacagg aacaucaaaa 1680

uccuauguaa ggucacucug augauaauag gcuggagccu cgguggccaa gcuucuugcc 1740

ccuugggccu ccccccagcc ccuccucccc uuccugcacc cguacccccg uggucuuuga 1800

auaaagucug aguggggcggc aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1860

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1920

ucuag 1925

<210> SEQ ID NO 75
<211> LENGTH: 2065
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 75

ucaagcuuuu ggacccucgu acagaagcua auacgacuca cuauagggaa auaagagaga 60

aaagaagagu aagaagaaau auaagagcca ccaugucacc gcaacgagac cggauaaaug 120

ccuucuacaa agauaacccu uaucccaagg gaaguaggau aguuauuaac agagaacauc 180

uuaugauuga cagacccuau guucugcugg cuguucuguu cgucauguuu cugagcuuga 240

ucggauugcu ggcaauugca ggcauuagac uucaucgggc agccaucuac accgcggaga 300

uccauaaaag ccucaguacc aaucuggaug ugacuaacuc caucgagcau caggucaagg 360

acgugcugac accacucuuu aaaaucaucg gggaugaagu gggccugaga acaccucaga 420

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gauucacuga ccuagugaaa uucaucucgg acaagauuaa auuccuuaau ccggauaggg 480

aguacgacuu cagagaucuc acuuggugca ucaacccgcc agagaggauc aaacuagauu 540

augaucaaua cugugcagau guggcugcug aagagcucau gaaugcauug gugaacucaa 600

cucuacugga gaccagaaca accacucagu uccuagcugu cucaaaggga aacugcucag 660

ggcccacuac aaucagaggu caauucucaa acaugucgcu guccuuguug gacuuguacu 720

uaggucgagg uuacaaugug ucaucuauag ucacuaugac aucccaggga auguaugggg 780

gaaccuaccu aguugaaaag ccuaaucuga acagcaaagg gucagaguug ucacaacuga 840

gcauguaccg aguguuugaa guagguguga ucagaaaccc gggguuuggg gcuccggugu 900

uccauaugac aaacuauuuu gagcaaccag ucaguaaugg ucucggcaac uguauggugg 960

cuuuggggga gcucaaacuc gcagcccuuu gucacgggga cgauucuauc auaauucccu 1020

aucagggauc agggaaaggu gucagcuucc agcucgucaa gcuggguguc uggaaauccc 1080

caaccgacau gcaauccugg gucccccuau caacggauga uccaguggua gacaggcuuu 1140

accucucauc ucacagaggu gucaucgcug acaaucaagc aaaaugggcu gucccgacaa 1200

cacgaacaga ugacaaguug cgaauggaga caugcuucca gcaggcgugu aaagguaaaa 1260

uccaagcacu cugcgagaau cccgaguggg uaccauugaa ggauaacagg auuccuucau 1320

acgggguccu gucuguugau cugagucuga cgguugagcu uaaaaucaaa auugcuucgg 1380

gauucgggcc auugaucaca cacggcucag ggauggaccu auacaaaucc aacugcaaca 1440

auguguauug gcugacuauu ccgccaauga gaaaucuagc cuuaggcgua aucaacacau 1500

uggaguggau accgagauuc aagguuaguc ccaaccucuu cacuguccca auuaaggaag 1560

caggcgaaga cugccaugcc ccaacauacc uaccugcgga gguggacggu gaugucaaac 1620

ucaguuccaa ccuggugauu cuaccugguc aagaucucca auauguuuug gcaaccuacg 1680

auaccuccag gguugagcau gcuguggguu auuacguuua cagcccaagc cgcucauuuu 1740

cuuacuuuua uccuuuuagg uugccuauaa aggggguccc aaucgaacua caaguggaau 1800

gcuucacaug ggaucaaaaa cucuggugcc gucacuucug ugugcuugcg gacucagaau 1860

ccgguggacu uaucacucac ucugggaugg ugggcauggg agucagcugc acagcuaccc 1920

gggaagaugg aaccaaucgc agauaaugau aauaggcugg agccucggug gccaagcuuc 1980

uugccccuug ggccuccccc cagccccucc uccccuuccu gcacccguac ccccgugguc 2040

uuugaauaaa gucugagugg gcggc 2065

<210> SEQ ID NO 76
<211> LENGTH: 1854
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 76

augucaccgc aacgagaccg gauaaaugcc uucuacaaag auaacccuua ucccaaggga 60

aguaggauag uuauuaacag agaacaucuu augauugaca gacccuaugu ucugcuggcu 120

guucuguucg ucauguuucu gagcuugauc ggauugcugg caauugcagg cauuagacuu 180

caucgggcag ccaucuacac cgcggagauc cauaaaagcc ucaguaccaa ucuggaugug 240

acuaacucca ucgagcauca ggucaaggac gugcugacac cacucuuuaa aaucaucggg 300

gaugaagugg gccugagaac accucagaga uucacugacc uagugaaauu caucucggac 360

aagauuaaau uccuuaaucc ggauagggag uacgacuuca gagaucucac uuggugcauc 420

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aacccgccag agaggaucaa acuagauuau gaucaauacu gugcagaugu ggcugcugaa 480

gagcucauga augcauuggu gaacucaacu cuacuggaga ccagaacaac cacucaguuc 540

cuagcugucu caaagggaaa cugcucaggg cccacuacaa ucagagguca auucucaaac 600

augucgcugu ccuuguugga cuuguacuua ggucgagguu acaauguguc aucuauaguc 660

acuaugacau cccagggaau guauggggga accuaccuag uugaaaagcc uaaucugaac 720

agcaaagggu cagaguuguc acaacugagc auguaccgag uguuugaagu aggugugauc 780

agaaacccgg guuugggggc uccgguguuc cauaugacaa acuauuuuga gcaaccaguc 840

aguaaugguc ucggcaacug uaugguggcu uuggggagc ucaaacucgc agcccuuugu 900

cacggggacg auucuaucau aauucccuau cagggaucag ggaaaggugu cagcuuccag 960

cucgucaagc ugggugucug gaaaucccca accgacaugc aauccugggu ccccuuauca 1020

acggaugauc caguggguaga caggcuuuac cucucaucuc acagaggugu caucgcugac 1080

aaucaagcaa aaugggcugu cccgacaaca cgaacagaug acaaguugcg aauggagaca 1140

ugcuuccagc aggcguguaa agguaaaauc caagcacucu gcgagaaucc cgagugggua 1200

ccauugaagg auaacaggau uccuucauac gggguccugu cuguugaucu gagucugacg 1260

guugagcuua aaaucaaaau ugcuucggga uucgggccau ugaucacaca cggcucaggg 1320

auggaccuau acaaauccaa cugcaacaau guguauuggc ugacuauucc gccaaugaga 1380

aaucuagccu uaggcguaau caacacauug gaguggauac cgagauucaa gguuagucccc 1440

aaccucuuca cugucccaau uaaggaagca ggcgaagacu gccaugcccc aacauaccua 1500

ccugcggagg uggacgguga ugucaaacuc aguuccaacc uggugauucu accuggucaa 1560

gaucuccaau auguuuuggc aaccuacgau accuccaggg uugagcaugc uguggguuau 1620

uacguuuaca gcccaagccg cucauuuucu uacuuuuauc cuuuuagguu gccuauaaag 1680

ggggucccaa ucgaacuaca aguggaaugc uucacauggg aucaaaaacu cuggugccgu 1740

cacuucugug ugcuugcgga cucagaaucc gguggacuua ucacucacuc ugggauggug 1800

ggcaugggag ucagcugcac agcuacccgg gaagauggaa ccaaucgcag auaa 1854

<210> SEQ ID NO 77
<211> LENGTH: 2126
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 77

ggggaaauaa gagagaaaag aagaguaaga agaaauauaa gagccaccau gucaccgcaa 60

cgagaccgga uaaaugccuu cuacaaagau aacccuuauc ccaagggaag uaggauaguu 120

auuaacagag aacaucuuau gauugacaga cccuauguuc ugcuggcugu ucuguucguc 180

auguuucuga gcuugaucgg auugcuggca auugcaggca uuagacuuca ucgggcagcc 240

aucuacaccg cggagaucca uaaaagccuc aguaccaauc uggaugugac uaacuccauc 300

gagcaucagg ucaaggacgu gcugacacca cucuuuaaaa ucaucgggga ugaagugggc 360

cugagaacac cucagagauu cacugaccua gugaaauuca ucucggacaa gauuaaauuc 420

cuuaauccgg auagggagua cgacuucaga gaucucacuu ggugcaucaa cccgccagag 480

aggaucaaac uagauuauga ucaauacugu gcagaugugg cugcugaaga gcucaugaau 540

gcauugguga acucaacucu acuggagacc agaacaacca cucaguuccu agcugucuca 600

-continued

aagggaaacu gcucagggcc cacuacaauc agaggucaau ucucaaacau gucgcugucc 660

uuguuggacu uguacuuagg ucgagguuac aaugugucau cuauagucac uaugacaucc 720

cagggaaugu auggggaac cuaccuaguu gaaaagccua aucugaacag caaaggguca 780

gaguugucac aacugagcau guaccgagug uuugaaguag gugugaucag aaacccgggu 840

uuggggcuc cgguguucca uaugacaaac uauuuugagc aaccagucag uaauggucuc 900

ggcaacugua ugguggcuuu gggggagcuc aaacucgcag cccuuuguca cggggacgau 960

ucuaucauaa uucccuauca gggaucaggg aaagguguca gcuuccagcu cgucaagcug 1020

ggugucugga aaucccaac cgacaugcaa uccugggucc ccuuaucaac ggaugaucca 1080

gugguagaca ggcuuuaccu cucaucucac agaggguguca ucgcugacaa ucaagcaaaa 1140

ugggcugucc cgacaacacg aacagaugac aaguugcgaa uggagacaug cuuccagcag 1200

gcguguaaag guaaaaucca agcacucugc gagaaucccg aguggguacc auugaaggau 1260

aacaggauuc cuucauacgg gguccugucu guugaucuga gucugacggu ugagcuuaaa 1320

aucaaaauug cuucgggauu cgggccauug aucacacacg gcucagggau ggaccuauac 1380

aaauccaacu gcaacaaugu guauuggcug acuauuccgc caaugagaaa ucuagccuua 1440

ggcguaauca acacauugga guggauaccg agauucaagg uuagucccaa ccucuucacu 1500

gucccaauua aggaagcagg cgaagacugc caugccccaa cauaccuacc ugcggaggug 1560

gacggugaug ucaaacucag uuccaaccug gugauucuac cuggucaaga ucuccaauau 1620

guuuuggcaa ccuacgauac cuccaggguu gagcaugcug ugguuuauua cguuuacagc 1680

ccaagccgcu cauuuucuua cuuuuauccu uuuagguugc cuauaaaggg ggucccaauc 1740

gaacuacaag uggaaugcuu cacaugggau caaaaacucu ggugccguca cuucugugug 1800

cuugcggacu cagaauccgg uggacuuauc acucacucug ggaugguggg caugggaguc 1860

agcugcacag cuacccggga agauggaacc aaucgcagau aaugauaaua ggcuggagcc 1920

ucgguggcca agcuucuugc cccuugggcc ucccccagc cccuccuccc cuuccugcac 1980

ccguaccccc guggucuuug aauaaagucu gagugggcgg caaaaaaaaa aaaaaaaaaa 2040

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2100

aaaaaaaaaa aaaaaaaaaa aucuag 2126

<210> SEQ ID NO 78
<211> LENGTH: 2065
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 78

ucaagcuuuu ggacccucgu acagaagcua auacgacuca cuauagggaa auaagagaga 60

aaagaagagu aagaagaaau auaagagcca ccaugucacc acaacgagac cggauaaaug 120

ccuucuacaa agacaacccc cauccuaagg gaaguaggau aguuauuaac agagaacauc 180

uuaugauuga uagaccuuau guuuugcugg cuguucuauu cgucauguuu cugagcuuga 240

ucggguugcu agccauugca ggcauuagac uucaucgggc agccaucuac accgcagaga 300

uccauaaaag ccucagcacc aaucuggaug uaacuaacuc aaucgagcau cagguuaagg 360

acgugcugac accacucuuc aagaucaucg gugaugaagu gggcuugagg acaccucaga 420

gauucacuga ccuagugaag uucaucucug acaagauuaa auuccuuaau ccggacaggg 480

aauacgacuu cagagaucuc acuuggugua ucaacccgcc agagagaauc aaauuggauu 540

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augaucaaua cugugcagau guggcugcug aagaacucau gaaugcauug gugaacucaa 600

cucuacugga gaccagggca accaaucagu uccuagcugu cucaaaggga aacugcucag 660

ggcccacuac aaucagaggc caauucucaa acaugucgcu gucccuguug gacuuguauu 720

uaagucgagg uuacaaugug ucaucuauag ucacuaugac aucccaggga auguacgggg 780

gaacuuaccu aguggaaaag ccuaaucuga gcagcaaagg gucagaguug ucacaacuga 840

gcaugcaccg aguguuugaa guagguguua ucagaaaucc gggguuuggg gcuccgguau 900

uccauaugac aaacuaucuu gagcaaccag ucaguaauga uuucagcaac ugcauggugg 960

cuuuggggga gcucaaguuc gcagcccucu gucacaggga agauucuauc acaauucccu 1020

aucagggauc agggaaaggu gucagcuucc agcuugucaa gcuagguguc uggaaauccc 1080

caaccgacau gcaauccugg gucccccuau caacggauga uccagugaua gacaggcuuu 1140

accucucauc ucacagaggc guuaucgcug acaaucaagc aaaaugggcu gucccgacaa 1200

cacggacaga ugacaaguug cgaauggaga caugcuucca gcaggcgugu aaggguaaaa 1260

uccaagcacu uugcgagaau cccgagugga caccauugaa ggauaacagg auuccuucau 1320

acggggucuu gucuguugau cugagucuga caguugagcu uaaaaucaaa auuguuucag 1380

gauucgggcc auugaucaca cacgguucag ggauggaccu auacaaaucc aaccacaaca 1440

auauguauug gcugacuauc ccgccaauga agaaccuggc cuuaggugua aucaacacau 1500

uggaguggau accgagauuc aagguuaguc ccaaccucuu cacuguucca auuaaggaag 1560

caggcgagga cugccaugcc ccaacauacc uaccugcgga gguggauggu gaugucaaac 1620

ucaguuccaa ucuggugauu cuaccugguc aagaucucca auauguucug gcaaccuacg 1680

auacuuccag aguugaacau gcuguaguuu auuacguuua cagcccaagc cgcucauuuu 1740

cuuacuuuua uccuuuuagg uugccuguaa gggggguccc cauugaauua caaguggaau 1800

gcuucacaug ggaccaaaaa cucuggugcc gucacuucug ugugcuugcg gacucagaau 1860

cugguggaca uaucacucac ucugggaugg ugggcauggg agucagcugc acagccacuc 1920

gggaagaugg aaccagccgc agauagugau aauaggcugg agccucggug gccaagcuuc 1980

uugccccuug ggccucccccc cagccccucc uccccuuccu gcacccguac ccccgugguc 2040

uuugaauaaa gucugagugg gcggc 2065

<210> SEQ ID NO 79
<211> LENGTH: 1854
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 79

augucaccac aacgagaccg gauaaaugcc uucuacaaag acaacccca uccuaaggga 60

aguaggauag uuauuaacag agaacaucuu augauugaua gaccuuaugu uuugcuggcu 120

guucuauucg ucauguuucu gagcuugauc ggguugcuag ccauugcagg cauuagacuu 180

caucgggcag ccaucuacac cgcagagauc cauaaaagcc ucagcaccaa ucuggaugua 240

acuaacucaa ucgagcauca gguuaaggac gugcugacac cacucuucaa gaucaucggu 300

gaugaagugg gcuugaggac accucagaga uucacugacc uagugaaguu caucucugac 360

aagauuaaau uccuuaaucc ggacagggaa uacgacuuca gagaucucac uugguguauc 420

aacccgccag agagaaucaa auuggauuau gaucaauacu gugcagaugu ggcugcugaa 480

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gaacucauga augcauuggu gaacucaacu cuacuggaga ccagggcaac caaucaguuc 540

cuagcugucu caaagggaaa cugcucaggg cccacuacaa ucagaggcca auucucaaac 600

augucgcugu cccuguugga cuuguauuua agucgagguu acaauguguc aucuauaguc 660

acuaugacau cccagggaau guacggggga acuuaccuag uggaaaagcc uaaucugagc 720

agcaaagggu cagaguuguc acaacugagc augcaccgag uguuugaagu agguguuauc 780

agaaauccgg guuuggggge uccgguauuc cauaugacaa acuaucuuga gcaaccaguc 840

aguaaugauu ucagcaacug caugguggcu uuggggagc ucaaguucgc agcccucugu 900

cacagggaag auucuaucac aauucccuau cagggaucag ggaaaggugu cagcuuccag 960

cuugucaagc uaggugucug gaaaucccca accgacaugc aauccugggu cccccuauca 1020

acggaugauc cagugauaga caggcuuuac cucucaucuc acagaggcgu uaucgcugac 1080

aaucaagcaa aaugggcugu cccgacaaca cggacagaug acaaguugcg aauggagaca 1140

ugcuuccagc aggcguguaa ggguaaaauc caagcacuuu gcgagaaucc cgaguggaca 1200

ccauugaagg auaacaggau uccuucauac ggggucuugu cuguugaucu gagucugaca 1260

guugagcuua aaaucaaaau uguuucagga uucgggccau ugaucacaca cgguucaggg 1320

auggaccuau acaaauccaa ccacaacaau auguauuggc ugacuauccc gccaaugaag 1380

aaccuggccu uagguguaau caacacauug gaguggauac cgagauucaa gguuaguccc 1440

aaccucuuca cuguuccaau uaaggaagca ggcgaggacu gccaugcccc aacauaccua 1500

ccugcggagg uggaugguga ugucaaacuc aguuccaauc uggugauucu accuggucaa 1560

gaucuccaau auguucuggc aaccuacgau acuuccagag uugaacaugc uguaguuuau 1620

uacguuuaca gcccaagccg cucauuuucu uacuuuuauc cuuuuagguu gccuguaagg 1680

ggggucccca uugaauuaca aguggaaugc uucacauggg accaaaaacu cuggugccgu 1740

cacuucugug ugcuugcgga cucagaaucu gguggacaua ucacucacuc ugggauggug 1800

ggcaugggag ucagcugcac agccacucgg gaagauggaa ccagccgcag auag 1854

<210> SEQ ID NO 80
<211> LENGTH: 2126
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 80

ggggaaauaa gagagaaaag aagaguaaga agaaauauaa gagccaccau gucaccacaa 60

cgagaccgga uaaaugccuu cuacaaagac aacccccauc cuaagggaag uaggauaguu 120

auuaacagag aacaucuuau gauugauaga ccuuauguuu ugcuggcugu ucuauucguc 180

auguuucuga gcuugaucgg guugcuagcc auugcaggca uuagacuuca ucgggcagcc 240

aucuacaccg cagagaucca uaaaagccuc agcaccaauc uggauguaac uaacucaauc 300

gagcaucagg uuaaggacgu gcugacacca cucuucaaga ucaucgguga ugaagugggc 360

uugaggacac cucagagauu cacugaccua gugaaguuca ucucugacaa gauuaaauuc 420

cuuaauccgg acagggaaua cgacuucaga gaucucacuu gguguaucaa cccgccagag 480

agaaucaaau uggauuauga ucaauacugu gcagaugugg cugcugaaga acucaugaau 540

gcauugguga acucaacucu acuggagacc agggcaacca aucaguuccu agcugucuca 600

aagggaaacu gcucagggcc cacuacaauc agaggccaau ucucaaacau gucgcugucc 660

cuguuggacu uguauuuaag ucgagguuac aaugugucau cuauagucac uaugacaucc 720

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cagggaaugu acgggggaac uuaccuagug gaaaagccua aucugagcag caaaggguca 780

gaguugucac aacugagcau gcaccgagug uuugaaguag guguuaucag aaauccgggu 840

uuggggguc cgguauucca uaugacaaac uaucuugagc aaccagucag uaaugauuuc 900

agcaacugca ugguggcuuu gggggagcuc aaguucgcag cccucuguca cagggaagau 960

ucuaucacaa uucccuauca gggaucaggg aaaggguguca gcuuccagcu ugucaagcua 1020

ggugucugga aaucccaac cgacaugcaa uccugggucc cccuaucaac ggaugaucca 1080

gugauagaca ggcuuuaccu cucaucucac agaggcguua ucgcugacaa ucaagcaaaa 1140

ugggcugucc cgacaacacg gacagaugac aaguugcgaa uggagacaug cuuccagcag 1200

gcguguaagg guaaaaucca agcacuuugc gagaaucccg aguggacacc auugaaggau 1260

aacaggauuc cuucauacgg ggucuugucu guugaucuga gucugacagu ugagcuuaaa 1320

aucaaaauug uuucaggauu cgggccauug aucacacacg guucagggau ggaccuauac 1380

aaauccaacc acaacaauau guauuggcug acuaucccgc caaugaagaa ccuggccuua 1440

gguguaauca acacauugga guggauaccg agauucaagg uuagucccaa ccucuucacu 1500

guuccaauua aggaagcagg cgaggacugc caugccccaa cauaccuacc ugcggaggug 1560

gauggugaug ucaaacucag uuccaaucug gugauucuac cuggucaaga ucuccaauau 1620

guucuggcaa ccuacgauac uuccagaguu gaacaugcug uaguuuauua cguuuacagc 1680

ccaagccgcu cauuuucuua cuuuuauccu uuuagguugc cuguaagggg ggucccccauu 1740

gaauuacaag uggaaugcuu cacaugggac caaaaacucu ggugccguca cuucugugug 1800

cuugcggacu cagaaucugg uggacauauc acucacucug ggaugguggg caugggaguc 1860

agcugcacag ccacucggga agauggaacc agccgcagau agugauaaua ggcuggagcc 1920

ucgguggcca agcuucuugc cccuugggcc ucccccagc cccuccuccc cuuccugcac 1980

ccguaccccc guggucuuug aauaaagucu gagugggcgg caaaaaaaaa aaaaaaaaaa 2040

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2100

aaaaaaaaaa aaaaaaaaaa aucuag 2126

<210> SEQ ID NO 81
<211> LENGTH: 1729
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 81

ucaagcuuuu ggacccucgu acagaagcua auacgacuca cuauagggaa auaagagaga 60

aaagaagagu aagaagaaau auaagagcca ccauggcaca agucauuaau acaaacagcc 120

ugucgcuguu gacccagaau aaccugaaca aaucccaguc cgcacugggc acugcuaucg 180

agcguuuguc uuccggucug cguaucaaca gcgcgaaaga cgaugcggca ggacaggcga 240

uugcuaaccg uuuuaccgcg aacaucaaag gucugacuca ggcuucccgu aacgcuaacg 300

acgguaucuc cauugcgcag accacugaag gcgcgcugaa cgaaaucaac aacaaccugc 360

agcgugugcg ugaacuggcg guucagucug cgaaugguac uaacucccag ucugaccucg 420

acuccaucca ggcugaaauc acccagcgcc ugaacgaaau cgaccgugua uccggccaga 480

cucaguucaa cggcgugaaa guccuggcgc aggacaacac ccugaccauc cagguuggug 540

ccaacgacgg ugaaacuauc gauauugauu uaaaagaaau cagcucuaaa acacugggac 600

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uugauaagcu uaauguccaa gaugccuaca ccccgaaaga aacugcugua accguugaua 660

aaacuaccua uaaaaauggu acagauccua uuacagccca gagcaauacu gauauccaaa 720

cugcaauugg cgguggugca acggggguua cuggggcuga uaucaaauuu aaagaugguc 780

aauacuauuu agauguuaaa ggcggugcuu cugcuggugu uuauaaagcc acuuaugaug 840

aaacuacaaa gaaaguuaau auugauacga cugauaaaac uccguuggca acugcggaag 900

cuacagcuau ucggggaacg gccacuauaa cccacaacca aauugcugaa guaacaaaag 960

aggguguuga uacgaccaca guugcggcuc aacuugcugc agcagggguu acuggcgccg 1020

auaaggacaa uacuagccuu guaaaacuau cguuugagga uaaaaacggu aagguuauug 1080

augguggcua ugcagugaaa augggcgacg auuucuaugc cgcuacauau gaugagaaaa 1140

caggugcaau uacugcuaaa accacuacuu auacagaugg uacuggcguu gcucaaacug 1200

gagcugugaa auuugguggc gcaaauggua aaucugaagu uguuacugcu accgauggua 1260

agacuuacuu agcaagcgac cuugacaaac auaacuucag aacaggcggu gagcuuaaag 1320

agguuaauac agauaagacu gaaaacccac ugcagaaaau ugaugcugcc uuggcacagg 1380

uugauacacu ucguucugac cugggugcgg uucagaaccg uuucaacucc gcuaucacca 1440

accugggcaa uaccguaaau aaccugucuu cugcccguag ccguaucgaa gauuccgacu 1500

acgcaaccga agucuccaac augucucgcg cgcagauucu gcagcaggcc gguaccuccg 1560

uucuggcgca ggcgaaccag guuccgcaaa acguccucuc uuuacugcgu ugauaauagg 1620

cuggagccuc gguggccaug cuucuugccc cuugggccuc cccccagccc cuccuccccu 1680

uccugcaccc guacccccgu ggucuuugaa uaaagucuga gugggcggc 1729

<210> SEQ ID NO 82
<211> LENGTH: 1518
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 82

auggcacaag ucauuaauac aaacagccug ucgcuguuga cccagaauaa ccugaacaaa 60

ucccaguccg cacugggcac ugcuaucgag cguuugucuu ccggucugcg uaucaacagc 120

gcgaaagacg augcggcagg acaggcgauu gcuaaccguu uuaccgcgaa caucaaaggu 180

cugacucagg cuucccguaa cgcuaacgac gguaucucca uugcgcagac cacugaaggc 240

gcgcugaacg aaaucaacaa caaccugcag cgugugcgug aacuggcggu ucagucugcg 300

aaugguacua acucccaguc ugaccucgac uccauccagg cugaaaucac ccagcgccug 360

aacgaaaucg accguguauc cggccagacu caguucaacg gcgugaaagu ccuggcgcag 420

gacaacaccc ugaccaucca gguuggugcc aacgacggug aaacuaucga uauugauuua 480

aaagaaauca gcucuaaaac acugggacuu gauaagcuua auguccaaga ugccuacacc 540

ccgaaagaaa cugcuguaac cguugauaaa acuaccuaua aaaaugguac agauccuauu 600

acagcccaga gcaauacuga uauccaaacu gcaauuggcg guggugcaac ggggguuacu 660

ggggcugaua ucaaauuuaa agauggucaa uacuauuuag auguuaaagg cggugcuucu 720

gcugguguuu auaaagccac uuaugaugaa acuacaaaga aaguuaauau ugauacgacu 780

gauaaaacuc cguuggcaac ugcggaagcu acagcuauuc ggggaacggc cacuauaacc 840

cacaaccaaa uugcugaagu aacaaaagag gguguugaua cgaccacagu ugcggcucaa 900

cuugcugcag caggggguac uggcgccgau aaggacaaua cuagccuugu aaaacuaucg 960

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uuugaggaua aaaacgguaa gguuauugau gguggcuaug cagugaaaau gggcgacgau 1020

uucuaugccg cuacauauga ugagaaaaca ggugcaauua cugcuaaaac cacuacuuau 1080

acagauggua cuggcguugc ucaaacugga gcugugaaau uugguggcgc aaaugguaaa 1140

ucugaaguug uuacugcuac cgaugguaag acuuacuuag caagcgaccu ugacaaacau 1200

aacuucagaa caggcgguga gcuuaaagag guuaauacag auaagacuga aaacccacug 1260

cagaaaauug augcugccuu ggcacagguu gauacacuuc guucugaccu gggugcgguu 1320

cagaaccguu ucaacuccgc uaucaccaac cugggcaaua ccguaaauaa ccugucuucu 1380

gcccguagcc guaucgaaga uuccgacuac gcaaccgaag ucuccaacau gucucgcgcg 1440

cagauucugc agcaggccgg uaccuccguu cuggcgcagg cgaaccaggu uccgcaaaac 1500

guccucucuu uacugcgu 1518

<210> SEQ ID NO 83
<211> LENGTH: 1790
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 83

ggggaaauaa gagagaaaag aagaguaaga agaaauauaa gagccaccau ggcacaaguc 60

auuaauacaa acagccuguc gcuguugacc cagaauaacc ugaacaaauc ccaguccgca 120

cugggcacug cuaucgagcg uuugucuucc ggucugcgua ucaacagcgc gaaagacgau 180

gcggcaggac aggcgauugc uaaccguuuu accgcgaaca ucaaaggucu gacucaggcu 240

ucccguaacg cuaacgacgg uaucuccauu gcgcagacca cugaaggcgc gcugaacgaa 300

aucaacaaca accugcagcg ugugcgugaa cuggcgguuc agucugcgaa ugguacuaac 360

ucccagucug accucgacuc cauccaggcu gaaaucaccc agcgccugaa cgaaaucgac 420

cguguauccg gccagacuca guucaacggc gugaaagucc uggcgcagga caacacccug 480

accauccagg uuggugccaa cgacggugaa acuaucgaua uugauuuaaa agaaaucagc 540

ucuaaaacac ugggacuuga uaagcuuaau guccaagaug ccuacacccc gaaagaaacu 600

gcuguaaccg uugauaaaac uaccuauaaa aaugguacag auccuauuac agcccagagc 660

aauacugaua uccaaacugc aauuggcggu ggugcaacgg ggguuacugg ggcugauauc 720

aaauuuaaag auggucaaua cuauuuagau guuaaaggcg gugcuucugc ugguguuuau 780

aaagccacuu augaugaaac uacaaagaaa guuaauauug auacgacuga uaaaacuccg 840

uuggcaacug cggaagcuac agcuauucgg ggaacggcca cuauaaccca caaccaaauu 900

gcugaaguaa caaaagaggg uguugauacg accacaguug cggcucaacu ugcugcagca 960

gggguuacug gcgccgauaa ggacaauacu agccuuguaa aacuaucguu ugaggauaaa 1020

aacgguaagg uuauugaugg uggcuaugca gugaaaaugg gcgacgauuu cuaugccgcu 1080

acauaugaug agaaaacagg ugcaauuacu gcuaaaacca cuacuuauac agaugguacu 1140

ggcguugcuc aaacuggagc ugugaaauuu gguggcgcaa augguaaauc ugaaguuguu 1200

acugcuaccg augguaagac uuacuuagca agcgaccuug acaaacauaa cuucagaaca 1260

ggcggugagc uuaaagaggu uaauacagau aagacugaaa acccacugca gaaaauugau 1320

gcugccuugg cacagguuga uacacuucgu ucugaccugg gugcgguuca gaaccguuuc 1380

aacuccgcua ucaccaaccu gggcaauacc guaaauaacc ugucuucugc ccguagccgu 1440

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aucgaagauu ccgacuacgc aaccgaaguc uccaacaugu cucgcgcgca gauucugcag 1500

caggccggua ccuccguucu ggcgcaggcg aaccagguuc cgcaaaacgu ccucucuuua 1560

cugcguugau aauaggcugg agccucggug gccaugcuuc uugccccuug ggccucccc 1620

cagccccucc uccccuuccu gcacccguac ccccgugguc uuugaauaaa gucugagugg 1680

gcggcaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1740

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaucuag 1790

<210> SEQ ID NO 84
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Salmonella typhimurium

<400> SEQUENCE: 84

Leu Gln Arg Val Arg Glu Leu Ala Val Gln Ser Ala Asn
1 5 10

<210> SEQ ID NO 85
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 85

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1 5 10 15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
20 25 30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
50 55 60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65 70 75 80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
85 90 95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
100 105 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Cys Lys Thr Ile
115 120 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
130 135 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Phe
145 150 155 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
165 170 175

Leu Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
180 185 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
210 215 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225 230 235 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe

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                245                 250                 255

Gly Ile Leu Cys Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 86
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 86

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
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65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Cys Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Cys Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu His Gln Trp His Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495
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Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 87
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 87

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Leu Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320
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Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 88
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 88

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Leu Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140
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Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asn Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 89
<211> LENGTH: 539
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 89

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1 5 10 15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
20 25 30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
50 55 60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Leu Lys Ser Ala Leu Arg Glu
65 70 75 80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
85 90 95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
100 105 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
115 120 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
130 135 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145 150 155 160

Ala Val Arg Glu Leu Lys Asp Phe Val Leu Lys Asn Leu Thr Arg Ala
165 170 175

Ile Asn Lys Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser
180 185 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
210 215 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225 230 235 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
245 250 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
260 265 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
275 280 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
290 295 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305 310 315 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
325 330 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
340 345 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
355 360 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
370 375 380

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Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 90
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 90

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Leu Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Leu Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205
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Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asn Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 91
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 91

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30
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Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Pro Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Leu Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
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    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 92
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 92

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Pro Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Leu Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
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        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asn Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 93
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 93

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Leu Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
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           100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525
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Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 94
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 94

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Leu Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350
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Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 95
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 95

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Leu Lys Asn Leu Thr Arg Ala
                165                 170                 175
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Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 96
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 96
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Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                  10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Trp Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415
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Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 97
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 97

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Leu Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Leu Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Leu Lys Asn Leu Trp Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240
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Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 98
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 98

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Pro Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60
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Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
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               485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 99
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 99

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
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305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 100
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 100

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
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    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Pro Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535
```

<210> SEQ ID NO 101

<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 101

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Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                  10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Pro Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380
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Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 102
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 102

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205
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Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Pro Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 103
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 103

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30
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Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445
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Ile Lys Phe Pro Glu Asn Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 104
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 104

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270
```

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Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Gln Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
        515                 520                 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
    530                 535


<210> SEQ ID NO 105
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 105

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
    50                  55                  60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95
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Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110

Ala Ala Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
        115                 120                 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Asn Asn Ala Leu Lys Lys Thr
    130                 135                 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145                 150                 155                 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
                165                 170                 175

Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
            180                 185                 190

Phe Ser Gln Trp Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195                 200                 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210                 215                 220

Ala Glu Leu Ala Arg Ala Val Pro Asn Met Pro Thr Ser Ala Gly Gln
225                 230                 235                 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245                 250                 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260                 265                 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
        275                 280                 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
    290                 295                 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305                 310                 315                 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325                 330                 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
            340                 345                 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355                 360                 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370                 375                 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385                 390                 395                 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445

Ile Lys Phe Pro Glu Asp Gln Phe Gln Val Ala Leu Asp Gln Val Phe
    450                 455                 460

Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465                 470                 475                 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
                485                 490                 495

Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
            500                 505                 510

Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
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515 520 525

Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
530 535

<210> SEQ ID NO 106
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 106

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tctgcaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccttt 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccct gaacaagaac 540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgtgt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcaa cgtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 107
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 107

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atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

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accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tctgcaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac 540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgtgt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagc accagtggca tgtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 108
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 108

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accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctgc tcaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

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gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac 540

aagtgcgaca tccctgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 109
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 109

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctgc tcaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac 540

aagtgcgaca tccctgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

-continued

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgaga accagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 110
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 110

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctgc tcaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgctt aagaacctga cacgggccat taacaagaac 540

aagtgcgaca tccctgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg 1380

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gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 111
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 111

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctgc tcaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgctt aagaacctga cacgggccat taacaagaac 540

aagtgcgaca tccctgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgaga accagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 112
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 112

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg cctgtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctgc tcaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac 540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 113
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 113

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg cctgtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctgc tcaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

-continued

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac 540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgaga accagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 114
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 114

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctgc tcaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac 540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

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ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac    840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc    900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac    960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga   1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc   1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc   1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc   1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc   1260

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cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg   1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc   1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg   1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc   1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac      1617


<210> SEQ ID NO 115
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 115

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gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga    120

accggctggt acaccaacgt gttcacactg gaagtgggcg acctcgagaa tctgacatgc    180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa    240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc    300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca    360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc    420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca    480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac    540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt    600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac    660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag    720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt    780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac    840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc    900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac    960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga   1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc   1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc   1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc   1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc   1260
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gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 116
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 116

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gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgctt aagaacctga cacgggccat taacaagaac 540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 117

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<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 117

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctgt ggcgggccat taacaagaac 540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 118
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 118

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acctcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctgc tcaagagcgc cctgagagaa 240

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ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc    300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca    360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc    420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca    480

gccgtgcgcg agctgaagga cttcgtgctt aagaacctgt ggcgggccat taacaagaac    540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt    600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac    660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag    720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt    780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac    840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc    900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac    960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga   1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc   1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc   1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc   1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc   1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga   1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg   1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc   1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg   1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc   1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac      1617
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<210> SEQ ID NO 119
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 119

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atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa     60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga    120

accggctggt acaccaacgt gttcacactg cctgtgggcg acgtcgagaa tctgacatgc    180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa    240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc    300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca    360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc    420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca    480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac    540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt    600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac    660
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ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 120
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 120

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac 540

aagtgcgaca tccctgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

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ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 121
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 121

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac 540

aagtgcccta tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

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accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 122
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 122

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg cctagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac 540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 123
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 123

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

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accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc    180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa    240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc    300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca    360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc    420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca    480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac    540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt    600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac    660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag    720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt    780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac    840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc    900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac    960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga   1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc   1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc   1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc   1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc   1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga   1320

cctgtgtcca gcagcttccc acctatcaag ttccctgagg atcagttcca ggtggccctg   1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc   1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg   1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc   1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac      1617
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<210> SEQ ID NO 124
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 124

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atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa     60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga    120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc    180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa    240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc    300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca    360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc    420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca    480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac    540
```

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aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgaga accagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 125
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 125

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac 540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagttcaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

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atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctcagg atcagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 126
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 126

atgagctgga aggtggtcat catcttcagc ctgctgatca cacctcagca cggcctgaaa 60

gagagctacc tggaagagtc ctgcagcacc atcacagagg gctacctgtc tgtgctgaga 120

accggctggt acaccaacgt gttcacactg gaagtgggcg acgtcgagaa tctgacatgc 180

tctgatggcc ctagcctgat caagaccgag ctggatctga ccaagagcgc cctgagagaa 240

ctcaagaccg tgtctgccga tcagctggcc agagaggaac agatcgagaa tcctggcagc 300

ggcagctttg tgctgggagc cattgctctt ggagtggctg ctgctgcagc tgttacagca 360

ggcgtggcca tcgctaagac catcagactg gaaagcgaag tgaccgccat caacaacgcc 420

ctgaagaaga caaacgaggc cgtcagcaca ctcggcaatg gcgttagagt gctggccaca 480

gccgtgcgcg agctgaagga cttcgtgtcc aagaacctga cacgggccat taacaagaac 540

aagtgcgaca tcgacgacct gaagatggcc gtgtccttta gccagtggaa ccggcggttt 600

ctgaacgtcg tgcggcagtt tagcgacaac gccggaatca caccagccat cagcctggac 660

ctgatgacag atgctgagct ggctagagcc gtgcctaaca tgcctacatc tgccggccag 720

atcaagctga tgctcgagaa tagagccatg gtccgacgga aaggcttcgg cattctgatt 780

ggcgtgtacg gcagcagcgt gatctatatg gtgcagctgc ctatcttcgg cgtgatcgac 840

acaccctgct ggattgtgaa ggccgctcct agctgtagcg agaagaaggg caattacgcc 900

tgcctgctga gagaggacca aggctggtat tgtcagaacg ccggcagcac cgtgtactac 960

cctaacgaga aggactgcga gacaagaggc gaccacgtgt tctgtgatac cgccgctgga 1020

atcaatgtgg ccgagcagag caaagagtgc aacatcaaca tcagcaccac caactatccc 1080

tgcaaggtgt ccaccggcag gcaccctatt tctatggtgg ctctgtctcc tctgggagcc 1140

ctggtggctt gttataaggg cgtgtcctgt agcatcggca gcaacagagt gggcatcatc 1200

aagcagctga acaagggctg cagctacatc accaaccagg acgccgatac cgtgaccatc 1260

gacaacaccg tgtatcagct gagcaaggtg gaaggcgaac agcacgtgat caagggcaga 1320

cctgtgtcca gcagcttcga ccctatcaag ttccctgagg atcagttcca ggtggccctg 1380

gaccaggtgt tcgagaacat cgagaattcc caggctctgg tggaccagtc caacagaatc 1440

-continued

ctgtctagcg ccgagaaggg aaacaccggc ttcatcatcg tgatcatcct gatcgccgtg 1500

ctgggcagct ccatgatcct ggtgtccatc ttcatcatta tcaagaagac caagaagccc 1560

accggcgctc ctccagaact gagcggagtg accaacaatg gcttcatccc tcacaac 1617

<210> SEQ ID NO 127
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 127

augagcugga agguggucau caucuucagc cugcugauca caccucagca cggccugaaa 60

gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaagugggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucuga ccaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucugcaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccuuu 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggcccu gaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugugu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucaa cguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 128
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 128

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augagcugga agguggucau caucuucagc cugcugauca caccucagca cggccugaaa 60

gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaaguggggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucuga ccaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucugcaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugugu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagc accaguggca uguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 129
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 129

augagcugga agguggucau caucuucagc cugcugauca caccucagca cggccugaaa 60

gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaaguggggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucugc ucaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

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cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucccugaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 130
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 130

augagcugga agguggucau caucuucagc cugcugauca caccucagca cggccugaaa 60

gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaagugggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucugc ucaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucccugaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

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ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac    960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga   1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc   1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc   1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc   1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc   1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga   1320

ccugugucca gcagcuucga cccuaucaag uucccugaga accaguucca gguggcccug   1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc   1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug   1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc   1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac      1617


<210> SEQ ID NO 131
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 131

augagcugga agguggucau caucuucagc cugcugauca caccucagca cggccugaaa     60

gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga    120

accggcuggu acaccaacgu guucacacug gaaguggggcg acgucgagaa ucugacaugc    180

ucugauggcc cuagccugau caagaccgag cuggaucugc ucaagagcgc ccugagagaa    240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc    300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca    360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc    420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca    480

gccgugcgcg agcugaagga cuucgugcuu aagaaccuga cacgggccau uaacaagaac    540

aagugcgaca ucccugaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu    600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac    660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag    720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu    780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac    840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc    900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac    960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga   1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc   1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc   1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc   1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc   1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga   1320
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ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 132
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 132

augagcugga agguggucau caucuucagc cugcugauca caccucagca cggccugaaa 60

gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaagugggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucugc ucaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugcuu aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucccugaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugaga accaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 133
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 133

augagcugga agguggucau caucuucagc cugcugauca caccucagca cggccugaaa 60

gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug ccugugggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucugc ucaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 134
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 134

augagcugga agguggucau caucuucagc cugcugauca caccucagca cggccugaaa 60

gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug ccugugggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucugc ucaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugaga accaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 135
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 135

augagcugga agguggucau caucuucagc cugcugauca caccucagca cggccugaaa 60

gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaagugggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucugc ucaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

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ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 136
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 136

augagcugga agguggucau caucuucagc cugcugauca caccucagca cggccugaaa 60

gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaagugggcg accucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucuga ccaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

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aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 137
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 137

augagcugga aggugucau caucuucagc cugcugauca caccucagca cggccugaaa 60

gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaaguggggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucuga ccaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugcuu aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

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<210> SEQ ID NO 138
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 138

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gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaagugggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucuga ccaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugucc aagaaccugu ggcgggccau uaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 139
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 139

augagcugga agguggucau caucuucagc cugcugauca caccucagca cggccugaaa 60

gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaagugggcg accucgagaa ucugacaugc 180

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ucugauggcc cuagccugau caagaccgag cuggaucugc ucaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugcuu aagaaccugu ggcgggccau uaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 140
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 140

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gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug ccuguggggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucuga ccaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

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```
cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag    720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu    780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac    840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc    900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac    960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga   1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc   1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc   1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc   1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc   1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga   1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug   1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc   1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug   1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc   1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac      1617
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<210> SEQ ID NO 141
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 141

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gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga    120

accggcuggu acaccaacgu guucacacug gaagugggcg acgucgagaa ucugacaugc    180

ucugauggcc cuagccugau caagaccgag cuggaucuga ccaagagcgc ccugagagaa    240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc    300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca    360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc    420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca    480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac    540

aagugcgaca ucccugaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu    600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac    660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag    720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu    780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac    840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc    900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac    960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga   1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc   1080
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ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 142
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 142

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gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaaguggggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucuga ccaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucguguc aagaaccuga cacgggccau uaacaagaac 540

aagugcccua ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

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accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 143
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 143

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gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaagugggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucuga ccaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug ccuagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 144
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 144

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accggcuggu acaccaacgu guucacacug gaagugggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucuga ccaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuuccc accuaucaag uucccugagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 145
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 145

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gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaagugggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucuga ccaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac 540

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aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugaga accaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 146
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 146

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gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaagugggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucuga ccaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguucaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

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ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccucagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

<210> SEQ ID NO 147
<211> LENGTH: 1617
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 147

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gagagcuacc uggaagaguc cugcagcacc aucacagagg gcuaccuguc ugugcugaga 120

accggcuggu acaccaacgu guucacacug gaagugggcg acgucgagaa ucugacaugc 180

ucugauggcc cuagccugau caagaccgag cuggaucuga ccaagagcgc ccugagagaa 240

cucaagaccg ugucugccga ucagcuggcc agagaggaac agaucgagaa uccuggcagc 300

ggcagcuuug ugcugggagc cauugcucuu ggaguggcug cugcugcagc uguuacagca 360

ggcguggcca ucgcuaagac caucagacug gaaagcgaag ugaccgccau caacaacgcc 420

cugaagaaga caaacgaggc cgucagcaca cucggcaaug gcguuagagu gcuggccaca 480

gccgugcgcg agcugaagga cuucgugucc aagaaccuga cacgggccau uaacaagaac 540

aagugcgaca ucgacgaccu gaagauggcc guguccuuua gccaguggaa ccggcgguuu 600

cugaacgucg ugcggcaguu uagcgacaac gccggaauca caccagccau cagccuggac 660

cugaugacag augcugagcu ggcuagagcc gugccuaaca ugccuacauc ugccggccag 720

aucaagcuga ugcucgagaa uagagccaug guccgacgga aaggcuucgg cauucugauu 780

ggcguguacg gcagcagcgu gaucuauaug gugcagcugc cuaucuucgg cgugaucgac 840

acacccugcu ggauugugaa ggccgcuccu agcuguagcg agaagaaggg caauuacgcc 900

ugccugcuga gagaggacca aggcugguau ugucagaacg ccggcagcac cguguacuac 960

ccuaacgaga aggacugcga gacaagaggc gaccacgugu ucugugauac cgccgcugga 1020

aucaaugugg ccgagcagag caaagagugc aacaucaaca ucagcaccac caacuauccc 1080

ugcaaggugu ccaccggcag gcacccuauu ucuauggugg cucugucucc ucugggagcc 1140

cugguggcuu guuauaaggg cguguccugu agcaucggca gcaacagagu gggcaucauc 1200

aagcagcuga acaagggcug cagcuacauc accaaccagg acgccgauac cgugaccauc 1260

gacaacaccg uguaucagcu gagcaaggug gaaggcgaac agcacgugau caagggcaga 1320

ccugugucca gcagcuucga cccuaucaag uucccugagg aucaguucca gguggcccug 1380

gaccaggugu ucgagaacau cgagaauucc caggcucugg uggaccaguc caacagaauc 1440

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cugucuagcg ccgagaaggg aaacaccggc uucaucaucg ugaucauccu gaucgccgug 1500

cugggcagcu ccaugauccu gguguccauc uucaucauua ucaagaagac caagaagccc 1560

accggcgcuc cuccagaacu gagcggagug accaacaaug gcuucauccc ucacaac 1617

What is claimed is:

1. A method comprising administering to a subject a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit formulated in a lipid nanoparticle in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit, wherein the lipid nanoparticle comprises 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid.

2. The method of claim **1**, wherein the open reading frame encodes a BetaCoV S protein.

3. The method of claim **2**, wherein the immune response is a neutralizing antibody response specific to the BetaCoV S protein.

4. The method of claim **1**, wherein the open reading frame encodes a BetaCoV S protein subunit selected from an S1 subunit and an S2 subunit.

5. The method of claim **4**, wherein the immune response is a neutralizing antibody response specific to the BetaCoV S protein subunit.

6. The method of claim **1**, wherein the mRNA formulated in a lipid nanoparticle is administered intramuscularly.

7. The method of claim **1**, wherein the mRNA further comprises a 5' untranslated region and a 3' untranslated region.

8. The method of claim **1**, wherein the mRNA further comprises a poly(A) tail.

9. The method of claim **1**, wherein the mRNA further comprises a 5' cap analog.

10. The method of claim **9**, wherein the 5' cap analog is 7mG(5')ppp(5')NlmpNp.

11. The method of claim **1**, wherein the mRNA comprises a chemical modification.

12. The method of claim **11**, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.

13. The method of claim **11**, wherein at least 80% of the uracil in the open reading frame of the mRNA has a chemical modification.

14. The method of claim **1**, wherein the lipid nanoparticle comprises 50 mol % ionizable cationic lipid, 10 mol % neutral lipid, 38.5 mol % cholesterol, and 1.5 mol % PEG-modified lipid.

15. The method of claim **1**, wherein the ionizable cationic lipid is Compound 25.

16. The method of claim **1**, wherein the neutral lipid is 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and the PEG-modified lipid is 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG-DMG).

17. A method comprising administering to a subject an mRNA comprising a 5' cap analog, a 5' untranslated region, an open reading frame encoding a BetaCoV S protein or S protein subunit, a 3' untranslated region, and a poly(A) tail formulated in a lipid nanoparticle in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit, wherein the lipid nanoparticle comprises 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid.

18. The method of claim **17**, wherein the open reading frame encodes a BetaCoV S protein.

19. The method of claim **18**, wherein the ionizable cationic lipid is Compound 25, the neutral lipid is DSPC, and the PEG-modified lipid is PEG-DMG.

20. The method of claim **18**, wherein at least 80% of the uracil in the open reading frame of the mRNA has a 1-methylpseudouridine modification.

21. The method of claim **20**, wherein the ionizable cationic lipid is Compound 25, the neutral lipid is DSPC, and the PEG-modified lipid is PEG-DMG.

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EXHIBIT 4

Company Name: Pfizer Inc
Company Ticker: PFE US Equity
Date: 2020-06-09

Goldman Sachs Virtual 41st Annual Global Healthcare Conference

Company Participants

- Albert Bourla, Chairman and Chief Executive Officer

Other Participants

- Terence Flynn, Analyst

Presentation

Terence Flynn {BIO 15030404 <GO>}

Great. Good afternoon, everybody. Thank you for joining us. I'm Terence Flynn, the Biopharma Analyst at Goldman Sachs. I'm very pleased to welcome Pfizer for this session. Joining us from the Company is Chairman and CEO, Albert Bourla.

Albert, thank you very much for joining us today. Really appreciate your time, and thank you for everything that the company is doing with respect to COVID-19 on both the vaccine and treatment front. I know it's a tremendous effort, and we appreciate everything you doing.

Albert Bourla {BIO 18495385 <GO>}

Thank you very much, Terence. And again, it's a great privilege and a great responsibility in these days to work on a solution.

Terence Flynn {BIO 15030404 <GO>}

Great. Maybe to get started, COVID-19 is obviously going to have near and long ranging impacts on the system, company's business models from delivery of care, clinical trial conducts, supply chain. Any preliminary perspective that you can share from kind of where you sit in terms of how this is going to change or evolve both the business and your strategy as you approach step forward?

Albert Bourla {BIO 18495385 <GO>}

Actually, I was reading earlier today, a report that you circulate about the, your assessment about how that could change the industry, and pretty much I agree with everything that you said. I think there are lot of trends that are emerging as a result of COVID. I think the fundamental that will impact our industry, it is the fact that right now the hopes of billions of people, hundreds of millions of businesses, hundreds of governments are on this

industry to find the solution. And that brings, obviously, the value proposition in the forefront of society, and that was not the case before, because there were a lot of lack popularity, and not very good reputation, and now is a great opportunity to -- of course to reset all this.

I won't declare any victory here, because I think the reputation comes in drops, but you can lose it in buckets. So it's going to be much slower to gain back and a mistake can also throw it out there, but I'm very optimistic with the way that the see the industry is moving. That said aside of the reputation of the industry, I think that brings also a lot of changes, some would be a very positive, some would be more or less on the negative side. I think local governments will likely value much more innovation, I can see I think much more premium based on the innovation right now.

On the other hand, I think there will be some fear that will drive more nationalization or in-sourcing, on-sourcing type of supply chains, that's a mistake. I think it's a very complicated supply chains, highly sophisticated. And by the way they were not on the -- they didn't present any issues, that's why, I think they were tested very well right now. I think on the -- perhaps it was a question of many people were asking me. I certainly see that there's a change shift right now particularly in the US. And I can see that both from people that they were very big fan of the innovations, I mean politicians or public servants that they were in front of -- in favor of the innovation but they were tempering their speech, now they are much more outspoken there because they see the value on the population, also I see it in people who were very strict critics of us, and they were criticizing a lot of the industry, I think they are slowing down.

They agree this is now and all of that is to do with the fact that there is a -- that the reputation, so as I said and the popularity is going up in the eyes of the positive sides. I can see structural changes might think in the way that we do research, I think with digital, pretty sure the question why only COVID will come, if we can make vaccines, if we prove that we can make vaccine in less than a year, okay, why can't we develop with other medicines with cancer medicines. And I think there is a -- I think that will give a very big boost in way about of life cycles of the productivity R&D will enhance and I can go on.

I think the post-COVID world will be different and hopefully get better.

Terence Flynn {BIO 15030404 <GO>}

Great. Well, that's a great place to start. I guess the other we're into June, a lot of states are starting to reopen, other countries are reopening. You guys have a big global presence, obviously you gave, you reiterated your expectations for guidance on your first quarter call.

Now that we're into June, can you just share a little bit about what you're seeing in some states and countries are reopening across the globe?

Albert Bourla {BIO 18495385 <GO>}

Yes. Everything we see, and that includes not only let's say the things that everybody is seeing, but also we are watching on our performance in the market month after month, et cetera, it's in line with what we were expecting at when we reiterated our guidance including absorbing significant amount for foreign exchange. And no exchange, I think we had a very, very good quarter in the first one, and we said the second is the one that will be the bottom of the crisis.

And I think, that will be the case, but still is holding very nicely, I think.

And then we hope that third and fourth will come back. The leading indicators, which is visits to physicians, new patient script, et cetera, et cetera already started to show a positive trend. And we are still in the second quarter, right. So the impact of that I think and also there is a lot of absorptions of inventories that maybe hospitals or others organizations, we never had stopped built in the first quarter at the wholesale is where control -- nothing, it was very, very small. So the performance was nothing to do with inventory that are control but, I suspect that may be hospitals or end-users, they were building some more, which I think will go away from the second quarter and then we'll have the full impact in third and fourth.

Terence Flynn {BIO 15030404 <GO>}

Okay, great. Maybe then the last COVID topic is just on the vaccine front. You've been partnered with BioNTech making a lot of progress. Maybe just remind us at a high level, the approach that you guys are taking and how it differs from some of the other companies? And then just any update in terms of when we might see the initial Phase 1 data? I know a lot of focus on that front as well.

Albert Bourla {BIO 18495385 <GO>}

Yeah, thank you. There are several efforts right now for vaccines as you know, what I know in the clinic, at least in the US, Europe, though there are three companies -- for and there are two different technologies. We are using an mRNA, modified RNA technology. I know that there is, but Moderna also is using the same technology. We are using four different approaches, that include the two different antigens, one antigen that we're using it is the entire spike protein, which is I think the same like the Moderna is using. And then we are using also the want we call the RBD, which is the head of the spike, the antigen. So we are using both just in case.

And then also, we are using three different constructs. We are using modified RNA, we are using unmodified enhanced RNA, and we are using several application. So not everything works the same, I can tell you that as we are in the clinic. So I think were -- it doesn't matter, the technology, I think you can have good or better results with the same technology. And we are well into humans now, and we are testing all of that and we will continue about to pick two of the four, so that we can continue. We are working also on the dose. I want -- as regards data, we keep seeing data both from pre-clinical data and clinical data from the humans.

I will not make any comments on the data what we see right now. We made a pledge that we will not speak publicly about how good or bad the vaccine is without the same day -- publishing date on Permagus [ph].

Terence Flynn {BIO 15030404 <GO>}

Okay.

Albert Bourla {BIO 18495385 <GO>}

But we do have plans to publish data. So once we publish the first data, we will speak about them, then I'll comment now about the vaccine and indeed, as I said at the end of June, we will have very good visibility of a lot of data. I want to reiterate again everything what I have said so far publicly for this vaccine. I just said that there are four -- there are going to be two. We are planning and we are in very good collaboration with FDA to run large scale trials July, August, if things go well, and it is so far, but you never know until the end. It's a very complicated process but if things goes well, we think that we will have enough data that will make us feel comfortable about the safety and efficacy.

And as a result, we'll submit to FDA, so that they can see if they feel comfortable with efficacy and safety in the October timeframe. So I think we can submit earlier to the FDA. So if that's the case so and FDA or EMA or others and ourselves I repeat because we are a very big organization, we're very careful of all these things, we feel good about safety and efficacy. We will have manufactured doses in lockdown [ph]. So we will be able in case we get either accelerate approval or emergency use approval and basically good, we could provide millions of doses this year and hundreds of millions of doses next year.

Again, I don't say how many exactly because I know others have spoken, because a lot depends what would be the dose. We are taking dose variations that 1 to 10. If we take 10 is less than if we take the one. We are trying to see if we can use multi-dose vials if that could be acceptable. For example, by US or different countries irrespective with them so that will -- they will define the quantities but definitely in the hundreds of millions in the worst case scenario.

Terence Flynn {BIO 15030404 <GO>}

Yeah. And just a follow-up on that, in terms of the amount of data, it sounds like the discussions are real time with regulators here, obviously safety is the most important. First thing to check. But in terms of efficacy, do you have any preliminary sense of kind of what they're looking for? Is this going to be tighter level data like immunogenicity or are they looking to see actual kind of infection rates from a study maybe somewhere in between?

Albert Bourla {BIO 18495385 <GO>}

I can't talk about for them. Right. I think they are independent and frankly, I think what they will do as always, they will have a holistic view of the situation. They will see how much efficacy data has, how much in primates, how much in humans. What is the titles. I think they will see everything and they will make decision themselves. I don't want to

speak about them. We are ready to go all the way to prove the -- say the efficacy in large scale trials if that is required. And this is what we are going to run.

Terence Flynn {BIO 15030404 <GO>}

Okay. And would you -- you mentioned that taking two of the four would then there be another choice where you choose one of those two to ramp up commercially if everything goes well, or do you think, you could ultimately maybe have two vaccines because obviously there is great demand across the board or what do you focus all of your efforts on one of those given scale.

Albert Bourla {BIO 18495385 <GO>}

I think, let me comment. I think would be likely huge demand and no matter how many companies will be able to cross the line still the demand will be higher than they offer that's my assessment right now, particularly for the first 12 months, let's say 21. The second is slightly will be big one of the two early enough and this is the one that we will push in our clinical trials and that we will do because I think two or one is the same in terms of manufacturing right. So I think we will exhaust our manufacturing capacity relevant if we do one or two, but we are going to work on the next generation but already started right now, but will not be the first wave, a much better hopefully but likely, we will come later in the game, let's say in '21 late, but right now, the things that we're speaking, we are speaking about likely one, but we will run into a very big clinical trial after doing all of this experiments and selecting different variations, but will give us safety and efficacy data.

Terence Flynn {BIO 15030404 <GO>}

Okay. And maybe the last one before we go on to another topic is just how do you think about, obviously there is a huge focus on treatments and vaccines in terms of the public health et cetera implications. How do you think about any longer term commercial opportunity here beyond the initial needs as you think about the kind of puts and takes on the commercial side of the equation?

Albert Bourla {BIO 18495385 <GO>}

Yes. One to start is that from day one, we said this is not business as usual. So our decision to go into the vaccine or not, was not driven at all by a return on investment. And I made it very clear to everyone. Okay it is a return on effort so what we are going to invest in it is things that we believe the effort could bring results, be relevant if we are going to get our money back or not. And actually, one of the reasons why we're the only company that didn't take any money from government, the US government and they were planned, available as you can read billions here and there or any other government per se, it is because we felt that we can move much faster if we are alone because when you take money, of course, you have to discuss how you spend it. How you progressed. How you do this How you do that And given that the goal was for return on effort, so we didn't factor in that we are going to take money or not.

Now as a result, the efforts -- the focus of me was always, let's bring a vaccine and then we speak later. So I was only been thinking about commercialization and if it commercial about now or later. But everybody is asking me. So I start thinking about it and again what I can tell it is that I do not think that, when the vaccine is available, if the vaccine is available and when. And by the way, I do feel that it's more a question of when rather than if but I say both to be on the safe side if and when. Likely the demand will be so big and likely, the value that the vaccine can bring, if we try to calculate the value of the vaccine for the pricing like any other vaccine we have, we can (inaudible) because obviously, you are having here now close economy or open economy right but if we were to implement three open market principles in pricing the product, we could go to huge surprises and sell everything we can manufacture, but would be unethical. We will not do it, right because that really taking advantage of a situation, people will not forget if you do that.

So I'm more into -- I think I would price, we will price the vaccine if it is available in the price of all the other vaccines that already exist in the market without taking into consideration the huge needs or the huge demand and offer, so that we will not have any type of this rumor. Still if you make the calculation, that's a huge commercial opportunity.

Terence Flynn {BIO 15030404 <GO>}

Okay, great. Appreciate the perspective and best of luck over the next several months. Then obviously other big picture topic, which is fairly relevant now is there is the pricing setback for Ibrance in adjuvant setting about a week ago and you reiterated your expectations for 6% top-line growth through 2025. I recognize, that's a risk adjusted figure so there is some puts and takes on either side. But how much pressure, does that really put on the other franchises that you guys have and maybe also on the other side of it on the inorganic side, how much pressure does it put on the M&A side, business development side of the equation as you think about reaching that 6% target.

Albert Bourla {BIO 18495385 <GO>}

Again I want to be very transparent and speak let's say, so first of all, I was surprised that PALLAS didn't make it in the interim result. I wasn't certain because it's a Phase III study, so you never if it works or not but is on everything that you had preclinically and in the mode of action, I never thought that will stop at the interim analysis for futility, so that's the trade of signs, but what it does into our overall portfolio and our growth trajectory, I had already said that is not I did the most to focus the company into science because I felt very good about, one, our R&D productivity. Again, the work of my predecessor and myself and Mikael Dolsten but it was under Ian that that was accomplished and because of the portfolio that we have right, it is very deepened. It has a lot of, it's very broad portfolio.

So on a risk adjusted basis is difficult to miss the 6% because if something fails, something items succeeds. So you take down the probability of that fails and you take up the probability of the one that is success. PALLAS for example because many peoples are asking, we had 50% probability of success in our models. And frankly, I don't do that often, but because of the importance we had $2 billion of big sales for PALLAS in addition

to the Ibrance and then risk adjusted one. And again, why we had all of that in our models was because the PALLAS could almost double the population which is addressable.

So that's one element, but also we temper that opportunity by the fact that the CDK penetration in a population that has very different risk profile, people were not dying or it was at best is having an adjuvant treatment, it's not taking something for someone who has a death sentence, right. So that was going to be much less, we're expecting that if we are successful competition will be successful on that and status were coming not far away one from another, unlike the first indication that it came years back. And also as we are very sophisticated in building our models, we knew that in the beginning we have a bulk of sales because there is a bonus but then the basis are recycle. If you treat them before, then you have less to treat when they -- that as well. With all of that in mind, that was the number what we had. So basically, for the 6% we had to absorb 1 billion right now. What happens of the time that we said the 6%. Many other things happened also on the positive side, we didn't have the Pneumococcal adult pivotal studies. As I said, if it is not pivotal, you have very low probabilities. So I mean if it's -- you can have 50% or whatever. When you go to a pivotal study positive and the probabilities are going much higher. In pediatric 20, by the way 20 adult we are going to fight this year. Right. So it's like we are the first to start.

Pediatric, we had pivotal, not -- we had proof of concept successful and we started pivotal already. We had the data, proof of concepts from Pneumococcal 20-Valent that we didn't have. We had proof of concept for RSV. We didn't have, we are starting pivotal studies allover. We had positive pivotal studies for abrocitinib, which is actually not one, more. So when we do that, so we took Ibrance from 50 to 0 in the pilot. And then we increased appropriately. The others into are still very good say for 6%.

Terence Flynn {BIO 15030404 <GO>}

Okay. And do you think are those the key opportunities that you think maybe investors are under-appreciating because I think consensus had probably, I would assume like higher Ibrance numbers. And so as a result, probably lower numbers than some of these other franchises. So as you look at those numbers, I know you're not giving product level guidance, but do you think that's kind of the key variable between, where the Street shaking out. And maybe where you guys are as you're optimistic about some of these other pipeline assets?

Albert Bourla {BIO 18495385 <GO>}

I'm optimistic, and I know there are many more. But I think right now, I have seen so far very little in the modeling. Prevnar for example I spoke, I think they have all model. So Prevnar 20 and adults and pediatric, they are all having it in their models, but I don't think anyone has Clostridium difficile, which is for a disease that doesn't have a vaccine, 30,000 people are dying every year from this disease.

Hence in the US only and we are expecting pivotal data this year, I don't think anyone has anything for pentavalent meningococcal, the first and only meningococcal vaccine that is in development right now and we have very strong Phase II data. Now, as I said in Phase

III. I don't think that anyone had any for RSV. Again, it is very strong. I don't think anyone is factoring and for the valent vaccine that we just licensed. In general, we have right now 7 vaccines, that they do not have another vaccine so they are first-in-class, all 7 in the clinic. Let me go to immuno-oncology. I think that everybody is factoring and modeling something on abrocitinib. I think everybody is missing the point. But right now, we have five different molecules in 10 different indications in immuno inflammation. Just to clarify and I will say it once more, we a very, very different strategy than anybody else who is jumping on JAKs right now because it's an attractive area, (inaudible) I would say, area. Everybody is having a strategy that they test molecules, they are picking a winner and then they develop this winner for all indications that's more or less the strategy or the other. We followed years back very different strategy. We are picking a single winner for an indication and for another indication another winner. And for the third, another winner because we have seen very big difference, very big difference when it comes to skin or when it comes to arthritis or when it comes to the gout et cetera.

So we believe, we're going to have best-in-class in all of that because of this approach. I don't think that everybody is again planning thafametis [ph] in the arthritis portfolio that we have. But no one is doing anything for Mofulia A [ph] and Mofulia B [ph] in terms of gene therapy or to say muscle dystrophin instead of gene therapy, maybe the same muscle dystrophy because there is a lot of debate, not because of us because what that means to the biotech that has a competing product and the whole block which has to begin. But this is why, some has debated, nobody is factoring anything on that. I can go on and on. Next week for example, we will release data and we will present and we will have also a big -- a quick let's say Investors Analyst review for internal medicine or GLP-1. So it's a lot of things that happened in oncology tremendous portfolio. So that's why, I think these are tangible assets. This is not things I have good vaccines portfolio. I have seven in clinical trials most of them in Phase III.

Yeah. So when they are first in class I think, that means something. I don't think still the Street is going into that detail. And I hope our Investor Day will make people see that, and I hope people will see earlier and the one-off missing opportunity.

Terence Flynn {BIO 15030404 <GO>}

Yeah. Great. Yeah, no, I think that will be a great opportunity to walk through a lot of this in September. I know you guys have prepared a lot for that and had to push it out obviously because of COVID -- to September, but really looking forward to the Investor Day in September. I guess the corollary, so it sounds, you're extremely confident in -- everything in the pipeline. So then what's the approach going to be on the business development front, obviously, you've done, you did the Array deal for bolt-on and brought in some revenues in cancer, also brings in some discovery engine, but what's the approach to M&A, here again, it sounds like you don't really feel like you need to do anything because of the depth of the pipeline. So how are you approaching the need for additional BD M&A?

Albert Bourla {BIO 18495385 <GO>}

Yeah, excellent question and it's exactly the same thing that I have said before, and let me reiterate because I want to be also realistic. I don't say that I feel extremely confident for everything in our pipeline, but I feel extremely confident for the pipeline as a whole because it has robust science multiple assets and appropriate risk adjusted. So I feel that statistics will work and we could have an upside, but I think statistics will work. Now what does this mean for our strategy in terms of business development, business development is not a strategy, it's a tool. So I want to start with all investors. It would be not to the interest of our shareholders if I say I'm excluding this or that. Everything, we never say never to anything. But also I want to be fair with also at investing and share my thoughts, my strategic thinking, how I see the growth in the business development. And it is what I say, I think, organically. I feel very confident right now, that we can go all the way to 26 with 6% growth.

Anything in business development that adds growth now is going to be just to make it higher, and this is, I don't think what or really we need right now, of course, we will do things, but it's not what we need. I think there is a lot of discussion what if this growth post 26 is sustainable and because products will start losing patent again. And I'm replying to them, I feel confident. First of all, it's normal the product we start losing. We're going to lose some, there are something altogether but it's all four, five years, four, five years period of time that those will happen. It's one every year, right. It's very normal to lose one patent every year.

Our internal pipeline, the way that we are planning it is that post 26 still we will have growth. But I think that to sustain that high level of growth, we are going to do business development, but includes Phase II, Phase III early assets, programs, research programs that will give us made this is potentially 23, 24, 25, 26 et cetera, so that they can propel the growth at this time.

Terence Flynn {BIO 15030404 <GO>}

Yeah, okay. And the core therapeutic areas you guys have talked about this at all. So I'm assuming no change on that front. And what -- the size of the deals, it sounds like more clinical stage is kind of really the core focus here as opposed to later stage commercial or larger deals, it sounds like that's again, given everything you've said that's completely off the table.

Albert Bourla {BIO 18495385 <GO>}

Yes, I think if you are speaking, as I said, nothing is over the table. I never say never, is not going to be interest of anyone to corner myself right, but I understand that people want to see what is a strategic thinking and you're right, it could be some, but they are on the later stage and likely will be more expensive, but the bulk of them will be on the Phase II, Phase III and yes. And now on the therapeutic areas. Again, I don't expect to have a significant changes in the therapeutic area, and there is one, yes, because, when we invest a lot on earlier science, you need to make sure that we invest in areas that you know your -- what you're doing.

I don't buy a product, but it's already done, so that I can only sell it and I'm confident on my commercial. In oncology vaccines, immune inflammation, rare disease, including gene therapy, internal medicines, metabolic diseases. Those are the five core areas. There are areas that will make -- we will make our scientist fewer mistakes and so letting the right assets and we will make way fewer mistakes in developing them because the development participant important than the potential of the molecule. So these are the areas I think that we will have the best return on investment right now.

We can do some here and there, but the major focus is -- is the areas that I just said.

Terence Flynn {BIO 15030404 <GO>}

Yeah, maybe a big picture kind of on the commercial side. In terms of your therapeutic areas. So you talked -- investors are fairly familiar with cancer, immunology in terms of how to think about these markets and the size of the potential market opportunity. Vaccines, I'd argue now, we as a society are probably going to be putting higher values on vaccines, given everything we've seen from COVID and it sounds like that's another big effort at Pfizer. Gene therapy is the one where I think there is maybe more of a debate in terms of understanding, kind of the commercial model, especially maybe if you're a second to market or third to market.

So how do you think about that commercial model evolving in gene therapy, obviously, it's another big important area for you. You're moving into Phase III for DMD and hemophilia as you mentioned. So how do you see the commercial model evolving? And how important is it to be first versus maybe the second with a better -- a better therapy.

Albert Bourla {BIO 18495385 <GO>}

Yeah, I think that the commercial model is still one of the unknowns. And there is -- one is because gene therapies are coming with a significant sticker shock. The tag price is very high. The value is very good, when you try to amortize but the fact that you have to pay it all upfront. It is going to create potential issue with payer not now because we have one or two. But if let's say, very big wave of them are coming. So I think this is something that everybody is recognizing and we are all trying to work on creative models, how the pricing could work and what happens if you can do in installments, if you can do it, going to be resolved, et cetera. Despite the fact that there is a little bit of uncertainty on the -- how the model will be developed. Myself, I have very high certainty, but it will develop and the reason is because the results of gene therapy are transformational. I don't know any other technology right now in development that gives the promise of such transformational therapeutic impact than the gene therapy. People that are living for years with hemophilia for example and particularly those are there in the high-risk groups, they have to do weekly injections right. Suddenly, these kids, they are getting one injection and they are in the fifth year and they are -- they are having 98% reduction of bleedings without going every week. Okay. That premium you can put to that. So when you have that or you are saying muscle dystrophy, kids that -- they have very prognosis and after the second decade of their lives, unfortunately, therefore they die most of them and they have very poor quality of life, we can't move, they can't eat, and when you have a product that with one injection improves dramatically that. I am sure that when the virus is there

society will find a way to pay for it. Now, is it going to be the first or the best that they will get everything, I really don't know. I think will be a lot of things that will be on play, your ability to manufacture, I think it's much more of a good question to ask right now in gene therapy because that seems to be bottleneck for everything, particularly when you came to muscle which requires significant volume. Gene therapies at the beginning work for eye only and that required very small quantity, you can do it in a lab.

Then you went to hemophilia, you speak much bigger quantity, because you need to target the liver. When you go to Duchenne or other, you go to much bigger volumes because you are talking about muscles. We have invested and right now, we have, I believe the largest manufacturing capacity under construction in North Carolina in the world for gene therapy and that not only will allow us to be in this area to provide for supply for our own products but makes us a partner of choice for smaller biotech that would like a partner, a middle partner, so that they can advance their position. And money everybody can give, manufacturing capacity, only those that they have, they can give. So I think that's also another advantage.

Terence Flynn {BIO 15030404 <GO>}

Great. Maybe in the last few minutes, we would just be curious and kind of as you think about the outlook for margins under kind of the new Pfizer, the biopharma business. How should we think about that evolving? Obviously, there are a number of puts and takes. It sounds like, you're going to do some additional streamlining, you've got new products coming on board. But then kind of back half of the decade. There are some other products coming off patent, do you feel pretty comfortable about being able to at least have flat margins kind of over that period. Maybe just at a high level, you could kind of talk about some of the puts and takes?

Albert Bourla {BIO 18495385 <GO>}

No, I didn't say that we will have flat. I think our margins will grow, will expand it. I think when your top-line, irrelevant what you do with your expenses, which set aside that for a moment. Okay. But in this business, in pharma, if your top-line grows 6%, there's only one name for bottom line, leverage, right. You need really to screw [ph] it big time, in the way you manage your P&L not to have lever. Now in addition to that and the fact that not only our 6 -- the top line is growing, but also the gross margin, because these are very innovative products and what we are going.

So the 6% is very innovative growth. So they have very high gross margins. Also we are going to attack, as we said, always the indirect SG&A expenses. And we have a very big program that we are trying to -- we are coming to a conclusion now that speaks about the enabling functions for a corporation like us. We have three core functions, every pharma company. We have a research engine function, makes all the products. We have a manufacturing, that produce them and then we have a commercial, make sure that there it's the patients.

But then we have in our case $4.5 billion annual expense in HR, legal, digital facilities, you name it. And this is the area that we try to make ourselves much more productive, not just

by cutting costs. But by imply -- by implementing simplification initiatives that will allow us to do -- to be much more effective and that will have also in addition to what I said about the top-line grow and will leverage on the bottom, that will be an additional boost to the bottom line.

Terence Flynn {BIO 15030404 <GO>}

Great. Great. Maybe just the last one, you mentioned your JAK portfolio and the confidence there and the differentiated approach, you're taking. Again, it is a fairly competitive area. But you do have a big presence with Celgene, you have a very deep pipeline. What's the kind of key differentiated feature as you see it? And how do you think about the competitive landscape from both other JAK inhibitors kind of these next gens, but also some of the biologics, like a drug like Dupixent, which you did a head to head study against?

Albert Bourla {BIO 18495385 <GO>}

Yeah. No. I think the best-in-class is what will win in this. That's why we took the strategy that we took at that time. And best-in-class is a combination of efficacy and safety profile. So and the more efficacious your molecule is typically the lower dose you have, so the less side effects, you will have to achieve the therapeutic effect. So by ourselves, this was the bet that we took by saying that let me find in preclinical and then proof of concepts which molecule work best for atopic dermatitis and by staying with that. And then I pick another one to do psoriasis even in the skin, right. We are using two different molecules. We do that because we see that in another one. We could have better as you guys have for psoriasis, which means that I can maintain the dose at a lower level. So to achieve the clinical results that are required without exposing let's say the safety. So I think given that will be a lot of -- there is a lot of research for that the best-in-class is what will make a very big difference.

Terence Flynn {BIO 15030404 <GO>}

Yeah. Great. And maybe just one email question, I got is, just as we think about the M&A environment, how do you think about valuations on kind of the biotech side now, things have come back, but any -- just high-level comments on biotech M&A?

Albert Bourla {BIO 18495385 <GO>}

I think they are very high and they -- as you said, a lot of them when the BARC [ph] went down and then some of them, I think they are coming back, but we need to understand that it's a very different story what is the market cap and what is the Board's perception of variable value, and although prices went down, what didn't follow it is the Board's let's say of different biotechs. They are still, I think some of them in denial. Okay, no, no it's much higher, but still so this a very expensive environment. We do have the means to play in this expensive environment but I want to be very careful how we spend the money. If we have to do -- to pay something that I think is on the edge of the variation because it really brings what we need. We will do it right, but I'm not going to -- to go to levels that I have

seen for the billions of dollars that were spent one molecule or maybe were negative, I don't like them.

Terence Flynn {BIO 15030404 <GO>}

Yeah. Okay, great. Well, I think we're up on time, Albert. But thank you so much for your comments. Really appreciate your time today. And again, thank you for everything you're doing on the COVID front and best of luck over the coming months and years.

Albert Bourla {BIO 18495385 <GO>}

No, Thank you very much and I will, finish with that. I hope all the companies are there working solutions right now, vaccines for example or the vials would be successful because it's much more likely than not but the demand will be so big that the offer cannot be coped, even if we are all approved.

Terence Flynn {BIO 15030404 <GO>}

Great, thank you. Thank you. Albert. Thank you, everybody.

Albert Bourla {BIO 18495385 <GO>}

Thank you, Terence.

EXHIBIT 5

Company Name: Pfizer Inc
Company Ticker: PFE US Equity
Date: 2020-05-19

RBC Capital Markets Global Healthcare Conference

Company Participants

- Chuck Triano, Vice President, Investor Relations

Other Participants

- Randall Stanicky, Analyst

Presentation

Randall Stanicky {BIO 6967011 <GO>}

Great. Thanks everybody for joining us for our next virtual fireside chat here. We're kicking things off again with our next company. I'm Randall Stanicky, the pharmaceuticals analyst here at RBC Capital Markets. And next up, we have Pfizer. The stock has proven resilient in the current pandemic. It's one of the names that we've been highlighting as defensive and wanting to own in this environment.

So with us to chat on the company current dynamics and outlook here, Senior Vice President of Investor Relations, Chuck Triano. And so Chuck, first, I just want to say thanks for joining us. It's great to have Pfizer at our conference. So thank you for that.

And then to start off, let's jump into DMD and the market opportunity. This was something that you guys sounded pretty excited about on Friday, relative to the data, you're pushing into Phase III early second half. To me, there seems to be more debate with investors around the competitive dynamics with Sarepta. So I have two questions. The first one, how do you think about the DMD market opportunity for Pfizer.

And again, I mean, you guys talk about scaling up here on a presumption of success, so maybe touch on that and then I have a follow-up.

Chuck Triano {BIO 3844941 <GO>}

Yeah, sure, sure. Yeah. And thanks for hosting the conference. So pleasure to be here. If we look at the prevalence, we see about 40,000 individuals effected with DMD in the developed countries. So within that 40,000 there is probably 10,000 to 12,000 affected in the US markets here, so certainly a significant market. Obviously very dire unmet medical need on that front and I'll maybe just add quickly that sometimes, one of the first questions that we get is just about gene therapy in general and whether it is a focus area for Pfizer or is it more just a one-off and I just want to really emphasize that the whole rare disease business inclusive of gene therapy is a very high priority for Pfizer. Right, as you're probably aware, we are stepping to therapeutic area business units, rare disease has its

own business unit, right, its own zone Chief Scientific Officer, Chief Development Officer, President.

So rare disease inclusive of gene therapy is a very high focus area for Pfizer. And even with DMD, we've talked about spending around $800 million of investment in manufacturing capacity down in North Carolina, so not just for the DMD program, but for some hemophilia programs as well. So this is a big area of focus for Pfizer and an important area. And I guess -- I just wanted to add that sometimes the first question I get is why is Pfizer in gene therapy? We are here, because we think -- we think we can -- we have a very comprehensive and a very competitive end-to-end capability between manufacturing, clinical trial development and then marketing, right. So we've been in rare disease for quite some time, have a lot of experience here, and this is one area where we think we are absolutely playing to one of our (Technical Difficulty). So I'll stop there and go onto your next questions and the topic.

Randall Stanicky {BIO 6967011 <GO>}

Yeah, I mean you're clearly committed and so there's a lot of focus on this program as the big driver within gene therapy and rare disease in general. So if you look at what we've heard coming out of Pfizer there is some debate around efficacy as you and Sarepta have used different study measures, you developed an LCMS method or mass spectrometry. Sarepta uses Western blot. But I thought you said probably you looked at both and I also think your patient age was slightly older which matters. How do you characterize your data versus Sarepta's understanding that they're not totally comparable?

Chuck Triano {BIO 3844941 <GO>}

Yeah and right. There's always the danger of cross-trial comparison. Right. So our mean age was a bit over 8-years-old and I think the first facts to point out is when you get into the older age group. This is where you're going to see some natural regression right. So you're going to see natural decline in the boys at that age as opposed to maybe in the 4 to 6-year-old age group, you're seeing natural improvement. Right. Regardless of any intervention. So as you have older boys, you are showing improvement in a cohort that you would expect to decline as opposed to showing improvement in an area where you would expect some improvement. So there is one difference there in terms of just the bandwidth of the ages that we looked at. For us, we have seen right now, we've shown the most comprehensive efficacy data for either program out there, very encouraging consistency in the results is what we've seen. And that's one big point I would stress for us is that consistency of the results.

Well we've used some different measurements, we mentioned -- we're using LCMS, which we view as more modern, more predictable, more accurate approach than Western blot. We did mention on the call that when we looked at Western -- looked at Western blot with some of our data in some instances, the readings exceeded 100% of the normal value of the CR [ph] assays.

So in terms of LCMS, we show it to be a much more qualitative measure of dystrophin levels -- higher -- more highly sensitive with good reproducibility and a wider dynamic

range. So we mentioned that we're talking with the agency and has been very encouraged. We're showing them our data and how we're measuring it, but we do see differences there. We have runs as we pointed out in the call, we have runs in Western blot, so we'll see what we do with that data, but that is also a difference in terms of how we're measuring.

So couple of apples versus oranges in a sense in terms of the comparability. But the encouraging consistency in the results is what we are happy to have. No need for high steroid use there and when we talk about the adverse events, we've had three that we reported, right, they happened early, they all rectified and once we saw those, we made some amendments to the protocol, where the protocol now is to look for complement activation and platelet reduction in the first two weeks with instructions to treat with an anti-complement drug as necessary. Right.

So the patients always don't need to be inpatient for this, since they are going to be monitored for liver function, they're not going to be too far away from a medical center anyhow and then I know -- we showed data on the nine boys, where we had the three SAEs that resolved. We've dosed an additional three, so we've got 12 boys dosed. We have not seen any additional SAEs at this point in the -- in the Phase 1b study.

So I think as we look at the view that this may be decades, if not a lifetime treatment versus the initial lead-in period of 14 days with with adverse events that were manageable on a benefit risk profile. That's why, we're very encouraged. Right. So again consistency in the results, manage and understand adverse events and the benefit that we can potentially provide these boys has us very bullish on the program. And as we mentioned, we're looking over the next several months that will start in the Phase 3 program that is planning to enroll 99 boys.

Again, this is the Phase 1b data more to come here, but in terms of what's out there to look at clearly the most comprehensive efficacy data of either of the studies, is that the data that we just showed.

Randall Stanicky {BIO 6967011 <GO>}

So that may stay in the under-appreciated pipeline bucket for now. And when launched in January, one of the biggest push backs was 2026 LOE and now 2026 and the current pandemic seems really, really far away, but one of the themes that did stick was you do have some under-appreciated pipeline and you guys have been wanting to discuss that. You push the Analyst Meeting for September for obvious reasons, given that the pandemic, but as you think about some of the things that Pfizer thinks that the Street is missing, what are those? You file tanezumab, you belt [ph] the PALLAS for citinib soon in atopic derm. The Street deals look warm on those, if you were to step back and say, okay, here are programs that Pfizer is most excited about, what would those be?

Chuck Triano {BIO 3844941 <GO>}

Yeah, sure, sure. Thanks. Yeah, it's interesting. Right the LOEs which start probably second half of 2026 and it's not that all of LOEs happen in 2026. Right, it's spread out between '26 and really '29. Paragraph one, sentence one is that if you are launching drugs on a regular basis. That's part of the business, right. So that's not a surprise. The fact that we don't have big efficacy for the next few years is more a reflection of (Technical Difficulty) R&D productivity 12 years ago, right, because we didn't have products to launch.

So for us having LOEs is not something that we say well that's really peculiar how are we going to manage that. And I'd also add, when we look at sell side models generally, the LOE cliff in totality, in the back half of the decade (Technical Difficulty) between $18 and $20 billion. I think we'd probably agree with that. But I'd also say, when we take a snapshot of our pipeline today and to your question, Randall. When we take a snapshot of the pipeline today. Again this is ignoring any future business development and just take a risk adjusted view of our pipeline. We have significantly more in terms of revenue generation from the pipeline, than what the projections are in terms of revenue lost.

And so if you look at the R&D Day, how we're and this goes right to your question, how we are determining what to focus with the shareholder base and investors and analysts with rather than saying we've got 70, 80, 90 programs look how many we have. This is about quality and so we made a couple of different cuts. We looked at compounds that we thought would be of most interest because one in almost all cases what we want to discuss launching by 2025 or at the end of 2025 or sooner. Right so this way, you can bring in compounds that would start to immuliarate LOEs. Two, we took a look at compounds -- again, this won't be all of them, but for many where we can show some new data, always easier to talk about why you're excited when you've got some data to show.

And then the third cut, we looked at our internal risk adjusted revenue projections for the -- for those compounds. And then we took a look at sell side models and we took the ones where there were the biggest gaps in terms of what we think on a risk adjusted basis and many of the sell-side models. And that we fully understand that from some compounds at NLSA [ph]. I haven't -- I'm aware of it, but I've seen no data. I haven't heard you talk about it, we don't expect that they're necessarily going to be modeling revenue. But just to run down if we've got, I don't know, 18 analysts or so, you mentioned abrocitinib right so.

Phase 3 data going to be filing I think about a third of the models have any revenue at all for abro. If I stick with the I&I, we've got our JAK3 TEC for alopecia. Right, this is post proof of concept in Phase 3 maybe a quarter of the sell-side models have any revenue at all there. If I look at our internal medicine area, which is probably an area in terms of the revenue potential, where we might see the biggest -- biggest potential in terms of single product, we have a post-proof of concept.

If you look at NASH a DGAT2 within ACC. Again, it's post proof of concept is -- are there any revenue in any models out there? No. We have the Akcea program right for high triglycerides, which is going to start a Phase -- moving toward Phase 3, not being modeled. If I look at gene therapy, right our hemophilia A, hemophilia B, again both programs that already have proof of concept, two or three models showing revenue at all

there. And then looking at our RSV maternal vaccine where on our earnings call, we mentioned, we just got positive Phase 2 data there that's not modeled at all.

And then the pentavalent meningococcal vaccine also post proof of concept, not being model. So a lot of companies like to talk about everything in their pipeline and I saw one analyst note that said. But most of the compounds these companies talk about are all pre-proof of concept highly risky. The ones I just listed are have proof of concept already.

So the thought is that we want to show you our work. We want to show the community why we're excited. We have up to the investment community to do their own homework and see if they agree,disagree, but we find it's always easier to -- to pick a meaningful and manageable number of compounds, show our work with some data, with some patient analytics, market sizes and then talk about how we see ourselves fitting in but that's usually the question that you just asked, what is Pfizer excited about, what is Pfizer focused on and why?

So I think when we get to the Analyst Day, we'll have a good -- a manageable number of compounds that we can deep dive and move there, but the short answer is right now, there is a lot that we have internally with -- with good risk adjusted profiles that are not yet being included in analyst models. So when people look at the quote cliff, it becomes a one-sided story externally. But that's why I say internally, we don't see it at all as a one-sided story. In fact, if anything, we see it more one-sided toward. We have more -- more than enough to replace with cell therapy [ph] and again that does not include any future business development.

So I'll stop there on that question.

Randall Stanicky {BIO 6967011 <GO>}

Yeah. And then if we pivot to what's probably definitely not in Street models. You can look at COVID-19 therapy or vaccine obviously with Moderna's update. A lot of focus around vaccines right now, but as we step back. There is also a lot of focus on where Pfizer is at. I think, Albert was recently quoted as saying, you guys could be in a position to deliver millions of vaccine doses of Bn1 sticks [ph] to by October and so just in light of some of the news flows the last couple of days, how are you guys thinking about COVID-19 from either a therapy or vaccine perspective.

Chuck Triano {BIO 3844941 <GO>}

Yeah. So we we've got both. We're in the clinics now with our partner BioNTech, right. And so we've got an mRNA vaccine and I'll say plural vaccines. We're testing four different variants of an mRNA vaccine. So we're testing, not just the spike protein, which we are testing, but we're not just testing that -- that's Moderna's approach, and I'm not saying that that's a bad approach at all, but in addition, we're testing, both the spike and the receptor binding domain. So which offers a different hypothesis and allows us then to select based on clinical data, the best one or two hypotheses to move forward here.

Right. So as we look at that, we are looking to dose just under 400 patients with each of the four variants of the vaccine. One is a self-amplifying version of that. We have two modified RNA and one with unmodified RNA. So we're looking at those and the plan would be -- as we move forward and I expect, we'll probably be in a position, and we've got our partnership here, so I can't commit to everything. But I would think by June sometime, we should be in a position to have some early antibody data there and presuming that one or two of the programs starts to show itself and emerge as probably a best hypothesis. We would look to move to sort of a Stage 2 of testing, where we'd get into now closer to 2500 patients and continue to add on the database.

And so that would run really through the summer time. And then after that, again, presuming things continue to go well and we're seeing a good profile emerge. We've said in the fall, we have probably close to 8,000 total participants on vaccine. We'd be manufacturing the lead-- lead candidate, we'd be manufacturing at risk. We'd be in a position to have tens of millions of doses if successful this year. And then hundreds of millions next year.

So really kind of growing the clinical study, reporting data maybe not quite real-time, but more of a back and forth with regulatory agencies in terms of as we get data in to supply them with data and we can do a much -- we think quicker analysis of the data. But I think our view having the four different variants of the MRNA vaccine, both the spike in the RBD, may be an advantage here. As we look to move quickly toward a vaccination.

We've got manufacturing capacity at our existing facilities there. So we're very, very hopeful that one of the four programs will look good. And then on antiviral, while we have screened out a lead compound. We've had some antivirals in our library back from SARS. They had not been in -- in preclinical tests at that point, but we had with the third party screened out and have looked to -- look and have identified a lead candidate that we'll start looking -- looking at that.

We're also looking at Xeljanz. There is a study going to occur in Italy at Xeljanz looking if there may be some impact on the cytokine storm that we're seeing, as part of the ramifications of COVID-19. So several irons in the fire here, Pfizer in terms of decision-making and resource allocation moving very, very quickly. And this is led from the top down from -- from the CEO level down doing everything we can to as safely and as quickly, look for vaccines or therapies here.

So the company is moving very, very quickly. The whole leadership team and clinical development team highly, highly focused here which is -- which is what you need, right.

You need a company and not just Pfizer but you need other companies, large companies that can make the investment that have the resources in terms of clinical studies manufacturing and look and if it doesn't work, we're not going to go out of business. Right. But we're able to put our best -- our best effort forward and just given the experience we have. We're very hopeful that we can -- we can get a therapy here.

Randall Stanicky {BIO 6967011 <GO>}

So a good case scenario has you in the market on a vaccine with millions of doses in October. At what point, would you be in scale up mode by a good part of the country?

Chuck Triano {BIO 3844941 <GO>}

So I think -- we thought -- we think if it's -- we'd have tens of millions, probably more and more in emergency use utilization and then we would look to see where is the (Technical Difficulty) and exposure there. And then as we look at next year, without giving exact numbers, we have said hundreds of millions of doses as we move into -- into 2021, so it's going to be interesting -- it's also, interesting indeed the one version, the one variant the self amplified some of the pre-clinical studies show that you could need up to maybe 50 times less dosing material for that compound. So that would really expand the ability.

But I think for us manufacturing into hundreds of millions is clearly a -- easily a 2021 event for us.

Randall Stanicky {BIO 6967011 <GO>}

Got it. We're in the last couple of minutes. But I did want to ask you just on business development outlook, look as you get past this Upjohn closing, you're going to have $12 billion in proceeds from Beatrice, you'll pay down debt with that that's going to bring debt down to net leverage of closer to call it 1.5 to sub 2 times and you're generating close to $10 billion in cash flow year. So the argument or the support to go do deals is there and I understand Pfizer's messaging right. There's no need to run out and do a big deal. That's only going to add to that the LOE issues in late 2020s when you could do mid to late-stage pipeline deals that can help you grow through that 2026 LOE.

How are you thinking now about deploying capital. I mean, should we be looking at Pfizer getting more aggressive coming out of this pandemic and are you seeing deals currently?

Chuck Triano {BIO 3844941 <GO>}

So I think we're -- I mean, we always see deals and I guess, there is no necessarily pattern that you have to follow meaning steady deals one a quarter or what have you, sometimes they seem to come in flurries as well. We just brought in a Lyme disease vaccine that's in Phase 2, right. So we've been doing -- we've done things in rare disease in vaccines. So we've been steadily building on what we know best. So when we look at deals, we are, for the most part, sticking to our key therapeutic areas because you are less likely to make mistakes. If you've got a real talented team in the rare disease with the vaccine or the I&I space, where you really know what to look for when you're looking to source externally. So again less likely to make mistakes as opposed to buying into an area that you don't know. So I think as when we focus on what we're looking at. Revenue now is not our issue, right.

We've said at least 6% on the top line, in terms of a revenue CAGAR, right. We were saying about 6, now we're saying at least 6% through the end of 2025. So it's not about bolting on revenue, now, right. That was more in the Hospira, the Medivation deals. It's

really looking to what your earlier question was about supplementing the internal pipeline for this back half of the decade. So that almost lends itself more often to doing licensing deals and maybe one-off deals for compounds that are in Phase II or so, that we can add a lot of value to given the expertise, if we stick with the areas that we have.

Look, we never say never. Right.

There is no upside to saying, we will never do something because you never know when the facts change or opportunities present themselves. But right now, our focus really is on the back half of the decade. And as a pure play biopharma company post Upjohn, right, it's all about the pipeline and you really want to -- you want to be carve yourself out as a real winner in a manageable number of therapeutic areas.

I think the old Pfizer way back right was in a lot of different therapeutic areas. But -- but didn't really commad many of them. So I think that's how we look at, look at BD. When I look at the $10 billion to $11 billion in cash flow, capital allocation and dividend, I'd say is very -- will remain an important part of the Pfizer story and a growing dividend. Right.

So that takes a big chunk of that cash flow, CapEx is probably a little less than $2 billion a year.

So that leaves you in terms of cash flow that's not allocated to either the dividend or CapEx. It leaves you know 1 billion to 2 billion leftover to redeploy in the business, now we can always borrow for opportunities, but if it is a bit of a different story as opposed to having $5 billion or $6 billion or $8 billion in cash flow, kind of left over after your dividend and CapEx every year.

So it's a different story. So, I think to our view, we're always looking, I think we do see a lot of interestings. I know we see a lot of interesting signs out there that we're -- that we're pursuing. And we've got a reputation now is becoming a very good partner is I'd say as opposed to a decade or 2 ago, where it was a different story here.

So again, we never say never to anything but again with our, I would echo what we've been saying, generally is that our main focus is to bolster the areas, where we already believe we have the right people, the right platform and we want to add more compounds into those areas.

Randall Stanicky {BIO 6967011 <GO>}

That's helpful color and probably a good place to end as well. We're a couple of minutes over. So I want Chuck -- thanks for joining us. We're glad we have Pfizer at our conference. And for those on the line. Our next session starts in three minutes, and that's the keynote with Dr. Scott Gottlieb, who coincidentally Chuck is also on the Pfizer board. So thanks, everyone.

Chuck Triano {BIO 3844941 <GO>}

Thanks, Randall. Thanks everybody for your attention. So long.

Randall Stanicky {BIO 6967011 <GO>}

Take care.

EXHIBIT 6

Company Name: BioNTech SE
Company Ticker: BNTX US Equity
Date: 2020-08-11

Q2 2020 Earnings Call

Company Participants

- Ozlem Tureci, Chief Medical Officer
- Ryan Richardson, Chief Strategy Officer, Managing Director & Member of Management Board
- Sean Marett, Chief Business Officer, Chief Commercial Officer & Member of Management Board
- Sierk Poetting, Chief Financial Officer, Chief Operating Officer & Member of Management Board
- Sylke Maas, Vice President, Investor Relations and Business Strategy
- Ugur Sahin, Co-Founder, Chief Executive Officer & Member of Management Board

Other Participants

- Analyst
- Arlinda Lee
- Daina Graybosch
- Matthew Holt
- Navin Jacob
- Olga Smolentseva
- Suzanne van Voorthuizen
- Zhiqiang Shu

Presentation

Operator

Thank you for standing by and welcome to the BioNTech Second Quarter 2020 Operational Progress and Financial Results Call. At this time, all participants are in a listen-only mode. There will a presentation followed by a question-and-answer session. I must advise you this call is being recorded today, Tuesday, the 11th of August 2020. And I would now like to hand the call over to the Vice President, Investor Relations and Business Strategy, Sylke Maas. Please go ahead.

Sylke Maas {BIO 20912536 <GO>}

Thank you for joining us today for BioNTech's Second Quarter 2020 Update Call. Before we start, we encourage you to view the slides for this webcast as well as operational and financial results press release issued this morning, both of which are accessible on our website, in the Investors section.

As shown on slide two, during today's presentation, we will be making several forward-looking statements. These forward-looking statements include but are not limited to the timing of enrollment, initiation, completion and reporting of data from our clinical trials, the potential registrational nature of certain clinical trials, the impacts of the COVID pandemic on our business and financial outlook. The timing for any potential emergency use authorizations or approvals for BNT162; the potential safety and efficacy of BNT162, and the ability of BioNTech to supply the quantities of BNT162 to support clinical development, and if approved, market demand, including our production estimates for 2020 and 2021.

Actual results could differ from those we currently anticipate. You are, therefore, cautioned not to place undue reliance on any forward-looking statements, which speak only as of the date of this conference call and webcast. Speaking and available for questions today will be Ugur Sahin, Chief Executive Officer; Ozlem Tureci, Chief Medical Officer; and Sean Marett, Chief Business and Commercial Officer; Sierk Poetting, Chief Financial and Operating Officer; and Ryan Richardson, Chief Strategy Officer.

I now hand the call over to Ugur Sahin, BioNTech's CEO.

Ugur Sahin {BIO 18869003 <GO>}

Thank you, Sylke. It's a pleasure to welcome you to our second quarter 2020 conference call. The last few months have been a game-changing time for BioNTech. The groundbreaking potential of our technologies, as well as our ability to quickly respond to new challenges and execute fast has been on full display. One key highlight is the initiation of the pivotal Phase 2b/3 trial of our lead BNT162 COVID-19 vaccine candidate within six months of starting the Lightspeed vaccine discovery preclinical and clinical research program.

In parallel to the COVID-19 program, we have continued to advance our oncology pipeline and broadened our base of strategic collaborations. I'm happy about the accomplishments we have made in the second quarter, and would like to thank our entire team and also our partners for their tireless efforts and outstanding commitment.

Slide five summarizes some of our key highlights since our last quarterly update. We reached a number of important milestones over the past few months. We continue to advance our clinical-stage pipeline. We now have 12 immunotherapies in clinical testing across three drug classes that includes eight messenger RNA therapeutic programs, three antibody programs and one small molecule immunomodulatory program.

In July, we and Pfizer selected BNT162b2 as our lead COVID-19 vaccine candidate and initiated a pivotal stage 2b/3 trial. We have made progress in granting up our manufacturing capacities to support global supply. We have signed commercial supply agreement with multiple countries around the world for more than 250 million doses in 2020 and 2021. This also includes an option to purchase up to 500 million additional doses; all this is subject to regulatory approval.

In parallel to our effort to bring COVID-19 vaccine to the market as quickly as possible, we also continued to advance our oncology pipeline. Ozlem will provide the key updates made on the call, including for our iNeST program, BNT122 or our BNT111 FixVac melanoma program. Here we announced a new cooperation with Regeneron to combine BNT111 with Libtayo an anti-PD-1 in a randomized Phase 2 trial, which we believe could have a registrational potential.

Moreover, we significantly strengthened our balance sheet, bringing in commitments of approximately $1.1 billion in gross proceeds from non-dilutive upfront cash payments and equity and debt financing commitments. These accomplishments have strengthened our ability to advance our pipeline on multiple fronts and deliver on our longer-term vision to bring novel immunotherapies to patients across a range of diseases.

Moving to slide six; I would like to touch on the importance of our strategic collaboration. This is important because these collaborations continue to play a crucial role in how we are building our business. Our partnership extend our execution capabilities and global reach, and in some cases, provide us the access to external technologies such as Genmab's DuoBody technology, which are highly complementary to our own.

The first half of 2020, we expanded our existing partnerships with Pfizer to jointly develop our COVID-19 vaccine program. In addition, we have established a new collaboration with Regeneron in the oncology field. The important aspect here is that we have retained significant economics on our programs through these collaborations. Sean will provide some further details on the Pfizer collaboration later in our prepared remarks. In the case of Regeneron deal, it is important to note that each party keeps 100% of the rights to its own product. That means that BioNTech has kept full product commercialization rights for BNT111 melanoma FixVac.

On slide seven, you'll see an updated version of our multi-platform, immuno-oncology strategy. The cornerstone of this strategy is to leverage our immunotherapy expertise with new therapeutic approaches to target cancer, and modulate immune responsive simultaneously. We believe, the approach can produce multiple blockbuster product opportunities, but also will enable the development of powerful combination treatment approaches, which combine complementary mechanisms of actions.

Despite the challenges associated with the COVID-19 pandemic, we have continued to execute our immuno-oncology strategy on multiple fronts. We are on track to initiate multiple late-stage trials for FixVac and iNeST product candidates. We are anticipating the first data update for our next generation checkpoint immunomodulator BNT311, a bi-specific antibody targeting anti-PD-L1/anti-4-1BB late this year.

Furthermore, since our last earnings call, we have initiated a Phase 1/2 trial for our TLR7 agonist small molecule immunomodulatory program and expect to initiate first-in-human trials for two novel cell therapy approaches in the coming months, including BNT211, an first CAR-T cell therapy and for BNT221, our neoantigen T cell therapy. As we have done in the past, we will continue to be data driven in how we assess each product opportunity we take into clinical testing.

I will now turn it over to Ozlem to provide an update on our programs.

Ozlem Tureci {BIO 20629996 <GO>}

Thank you, Ugur. In the interest of time, I'm going to focus my remarks to the four programs highlighted on slide nine. These include BNT111, our FixVac melanoma; BNT122, our iNeST program; BNT311, our anti-PD-L1/anti-4-1BB antibody; and BNT411, our TLR7 agonist. For further details on the status of other programs, please refer to our full quarterly update, which will be released -- which was released this morning.

So let's start on slide 10 with BNT111, our melanoma FixVac program. As a reminder, BNT111 is composed of four non-mutated melanoma antigens. NY-ESO-1; MAGE-A3; tyrosinase and a novel antigen from our own libraries TPTE. In July, we published interim Phase 1 data in Nature from our ongoing Lipo-MERIT trial. The Lipo-MERIT trial is a multi-center, open label dose escalation study to evaluate safety and tolerability of vaccinated patients with Stage IIIbc and Stage IV melanoma.

Efficacy was evaluated in a subset of 42 checkpoint-inhibitor experienced patients with a data cutoff in July 2019. As I reported earlier, at the data extraction date, three patients out of 25 in the FixVac monotherapy group experienced a partial response. Seven patients showed stable disease and one patient showed a complete metabolic remission of metastatic lesions. Of the 17 patients treated with the combination of FixVac of BNT111 and an anti-PD-1, six patients showed a partial response.

Of note, at our target dose for the Phase 2 trial of 100 micrograms, we observed that five of 10 patients had a partial response to FixVac in combination with anti-PD-1 therapy. The publication in nature summarized on slide 11 highlighted extensive biomarker and immunological data. These support the mechanism of action and the observed clinical activity of FixVac alone and in combination with anti-PD-1.

Importantly, treatment with BNT111 resulted in the expansion and activation of circulating tumor antigen specific T-cells with memory function that exhibited strong cytotoxic activity against tumor cells. These vaccine-induced T-cells displayed a Th1 phenotype. In 20 patients tested by post IVS interferon-gamma ELISpot, all showed immune response against at least one of the used tumor-associated antigens. Most patients demonstrated CD4 or concurrent CD4 and CD8 T-cell responses.

In 50 patients tested by ex vivo interferon-gamma ELISpot, which only captures high magnitude responses, more than 75% of patients showed immune responses against at least one tumor-associated antigen, most of which were high magnitude CD8 positive T cells. T-cells ramped up within four to eight weeks to single digit or low-double digit percentages of total circulating CD8 positive T-cells. Under monthly maintenance treatment, the levels of T-cells continued to slowly increase or remain stable up to over one year.

Safety was assessed in 89 patients. Overall, FixVac treatment was well tolerated with no dose-limiting toxicity observed. Most common adverse events were mild-to-moderate,

transient flu-like symptoms, such as pyrexia and chills. As Ugur mentioned earlier, we recently announced a strategic collaboration with Regeneron and plan to pursue an accelerated development program for the combination of FixVac and Regeneron anti-PD-1 agent Libtayo in the second line treatment setting for advanced melanoma patients that have progressed after prior PD-1 blockade.

Under the terms of agreement, we and Regeneron have agreed to share development costs equally. If approved, each party will retain full commercial rights for their respective product and would record revenues related to its own product. We plan to initiate a randomized Phase 2 trial in the fourth quarter of 2020 and expect to provide more details on the study in the third quarter 2020.

Now moving to slide 12 to BNT122, our individualized neoantigen specific immunotherapy or iNeST platform program, which is partnered with Roche Genentech. The data updates for the Phase 1a monotherapy and 1b combination with Tecentriq basket trials in multiple solid tumors was reported in June as part of AACR virtual annual meeting, too. This is the first time that we have shown safety and immunogenicity data across different tumor types outside of melanoma.

The patient populations in these cohorts were heavily pretreated many with refractory and recurrent disease with a high proportion of low PD-L1 expresser. Treatment with BNT122 alone and in combination with Tecentriq was well tolerated with the majority of adverse events being Grade 1 or Grade 2 and there were no dose limiting toxicities. In the majority of patients treated with BNT122 alone and in combination with Tecentriq, ex-vivo T-cell responses against multiple neoantigens were detected. We also detected BNT122-induced T-cells in infiltrates of patient tumors.

In the Phase 1a immunotherapy portion of the trial, 26 patients underwent at least one tumor assessment, one patient (inaudible) with gastric cancer and metastatic liver lesions had a durable complete response and remains on study after 1.5 years and the rest patients had stable disease. In the Phase 1b combination portion of the trial, in 108 patients that underwent at least one tumor assessment, one patient had a complete response, eight patients had partial responses, and 53 patients had stable disease.

We continue to believe that iNeST is well suited to earlier lines of therapy across a range of solid tumors. We have depicted our ongoing Phase 2 trial in first line melanoma and our planned adjuvant [ph] clinical trial for iNeST. On slide 13, we expect to provide an enrollment update from the randomized Phase 2 trial of BNT122 plus pembrolizumab in first line melanoma in the second half of 2020 and an interim data update is anticipated in the second half of 2021.

We are going to start two Phase 2 studies in the adjuvant setting. One is in an IO sensitive cancer type, namely evaluating the efficacy and safety of iNeST plus Tecentriq compared with Tecentriq alone in patients with early and adjuvant stage non-small-cell lung cancer. The second study is in an IO insensitive cancer type namely a multisite open-label Phase 2 randomized trial to compare the efficacy of iNeST versus watchful waiting in patients with circulating tumor DNA positive Stage 2 high-risk and Stage 3 colon cancer.

Now moving to slide 14 to the two DuoBody programs, we have partnered with Genmab. On slide 15, you'll see one of them, BNT311, the anti-PD-L1-anti-4-1BB bi-specific antibody that combine constitutive TPI blockade and conditional costimulatory activity. A mechanism of action which led to enhanced proliferation of antigen-specific activated T-cells in the presence of PD-L1 positive cells in preclinical studies.

Based on the preclinical data we have generated, we believe, this molecule could represent a powerful new checkpoint immune modulator with seropositive potential across a range of solid tumors. We expect to provide the first human data in the second half of 2020. This update will include dose escalations data from the Phase 1/2 trial in multiple target tumors. We believe it has broad potential in a range of solid tumors, including those where checkpoint therapy is currently established, but also in more difficult tumors where first generation checkpoint inhibitors have not been as successful.

Finally now turning to slide 16; we recently initiated clinical testing for BNT411 from our toll-like receptor binding program. This molecule is engineered for high potency and has high selectivity for the TLR7 receptor at the therapeutically active dose range. We expect this molecule to activate both the adaptive and innate immune system, in particular, in combination with cytotoxic therapies and checkpoint inhibitors.

Preclinical studies suggest a Type 1 interferon-dominated release of cytokines and chemokines and potent stimulation of antigen-specific CD8 T-cells, but also B cells details, and innate immune cells such as NK cells and macrophages. In early July 2020, the first patient was dosed in the Phase 1/2a first-in-human open-label dose escalation trial with expansion cohorts to evaluate the safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy.

BNT411 will be posted as the monotherapy in patients with solid tumors and in combination with Tecentriq, carboplatin and etoposide in patients with chemotherapy-naive extensive-stage small cell lung cancer. Now these were the highlights from our oncology programs. I now provide an update on our COVID-19 vaccine program.

Now moving to slide 18, which recaps how far we have come in the race to develop a COVID-19 vaccine. We began work on multiple vaccine candidates in late January following use of the coronavirus outbreak in China. Approximately six months later, we initiated a pivotal Phase 2b/3 trial aimed at supporting an approval of our vaccine in the U.S. Our goal with Pfizer is to be in a position to file for approval or emergency authorization from the FDA as early as the fourth quarter of 2020, if the trial hits our enrollment targets and is deemed to be successful. I will come back to the Phase 2b/3 trial design in a few minutes.

On slide 19 you see the four vaccine variance we have taken into clinical testing. These variants vary based on the type of mRNA construct used and the antigen target, two of variance target for RBD domain and the other two the full-length spike protein. Both our b1 and b2 candidates have received FDA fast-track status. In late July, we along with Pfizer selected BNT162b2 to as our lead candidate for Phase 2b/3 trail.

BNT162b2 encodes for a modified version of a full-spike protein and utilizes our nucleosidemodified RNA construct. The decision to advance the BNT162b2 was made after an extensive review of a preclinical and available clinical data and in consultation with the FDA. For the Phase 2b/3 trial, the 30 microgram dose level in a two-dose regimen was chosen.

Now moving to slide 20; BNT162b2 vaccinated participants displayed a favorable breadth of epitopes recognized in T-cell responses specific to the SARS-CoV-2 antigen. The candidate also demonstrated concurrent induction of both high-magnitude CD4 and CD8 T-cell responses. These T-cell responses were observed against both the RBD and the remainder of the spike glycoprotein. We believe that immune recognition of more spike T-cell epitopes may have the potential to generate more consistent responses across diverse populations and in older adults.

Preliminary data for BNT162b2 suggested a favorable reactogenicity profile. Systemic events were generally mild to moderate and transient, lasting one to two days. Events included fever, fatigue, and chills. There has not been any serious adverse events observed in our BNT162 program. Data collection from the Phase 1/2 trial for all four vaccine candidates is continuing. We plan to submit data on BNT162b2 for peer review and potential publication in the next few weeks. We also intend to also post the manuscripts on the preprint server at that time.

Moving to slide 21; I'd like to spend a few minutes to outline the design of our ongoing Phase 2b/3 trials. The study is expected to enroll up to 30,000 participants age 18 to 85 years, starting in the U.S., and expanding to include approximately 120 sites globally. The trial regions will include areas with significant anticipated SARS-CoV-2 transmission. The Phase 2b/3 trial is a one-to-one vaccine candidate to placebo randomized observer blinded study to obtain the safety, immune response and efficacy data needed for regulatory review.

The primary endpoint is prevention of COVID-19 in participants without evidence of SARS-CoV-2 infection before vaccination, as well as prevention of COVID-19 in participants regardless of SARS-CoV-2 infection before vaccination. The primary efficacy analysis will be an event-driven analysis based on the number of participants with symptomatic COVID-19 disease. We reduced polymerase chain reaction to confirm infection of SARS-CoV-2 since antibody tests to confirm previous exposure. One of the secondary endpoints includes prevention of severe COVID-19 disease. The trial design allows for interim analysis and un-blinded reviews by an independent external data monitoring committee. Assuming clinical success, we along with Pfizer may potentially seek regulatory review in Q4, as early as October 2020.

With that, I will now hand over to Sean to provide an overview on our commercial updates.

Sean Marett {BIO 5299154 <GO>}

Thank you, Ozlem. I will start by recapping our commercial arrangements for BNT162 with Pfizer and Fosun. Depicted on slide 22, our collaboration with Pfizer involves co-development of a portfolio of COVID-19 vaccine candidates on a worldwide basis, excluding China. Upon approval, we would jointly commercialize the vaccine with Pfizer.

As part of our preparation for commercialization, BioNTech is taking steps to establish a limited commercial infrastructure in a selected set of countries, while leveraging Pfizer's commercial infrastructure and capabilities in the rest of the world, excluding China, as I just noted. In terms of financials, our collaboration with Pfizer is based on a 50-50 partnership. Both companies share development expenses and gross profits worldwide on a 50-50 basis, regardless of which company distributes the vaccine in a given country.

Furthermore, capital expenditures are funded by each party independently. In addition to the combined upfront payment and equity investment of $185 million, which BioNTech received in April, BioNTech is eligible to receive further development in sales milestones of up to $563 million. If reached, these milestones will come in addition to BioNTech's 50% share of gross profits generated. Our Fosun collaboration in China is also a co-development agreement.

However, Fosun funds the majority of development expenses incurred in China and would take on commercialization responsibilities if the vaccine is approved. In addition to the combined upfront payment and the equity investment totaling $51 million, which was received in April, BioNTech is eligible to receive further development and sales milestones up to $84 million. BioNTech would also share gross profits on the sale of the vaccine in China.

I will now turn to slide 23 to provide an overview of our recently-announced commercial supply agreements. From the beginning, we have been very clear about our intention to make our vaccines available for global supply to address the pandemic. And we are investing at risk to scale up our manufacturing to enable us to do so. BioNTech and Pfizer have a target to manufacture up to 100 million doses by the end of 2020, and approximately 1.3 billion doses by the end of 2021.

This estimate presumes a continued ramp-up in production at our Idar-Oberstein and Mainz facilities in Germany, which are currently producing vaccines for clinical supply. We're also working with Pfizer to activate and ramp-up vaccine production at several Pfizer sites in the United States and one in Europe. While it is still early, we have announced commercial supply agreements with the governments of multiple countries for more than 250 million doses with an option for an additional 500 million doses.

Furthermore, we are currently in a number of discussions with governments around the world in relation to further commercial supply. All agreements are subject to clinical success and regulatory approval of the vaccine.

I will now hand over to Sierk it to provide an update on our financials.

Sierk Poetting {BIO 21288849 <GO>}

Thank you, Sean. Now, I would like to summarize our financial results for the quarter that are shown on slide 25. Our total revenue, which primarily consists of revenue from our collaboration agreements, was EUR41.8 million for the second quarter 2020 compared to EUR25.8 million for the second quarter 2019. For the period of six months ended June 30, 2020, our total revenue was EUR69.4 million compared to EUR51.9 million for the comparative prior-year period.

The revenue from collaboration agreements overall increased due to the recognition of revenue from our new collaboration agreement signed with Pfizer and Fosun Pharma as part of our BNT162 vaccine program against COVID-19. The revenues from other sales transactions increased due to increased orders and include sales of diagnostic products, peptides, retroviral vectors for clinical supply and development and manufacturing services sold to third-party customers.

Research and development expenses were EUR95.2 million for the second quarter 2020 compared to EUR53.4 million for the second quarter 2019. For the six month ended June 30, 2020, total research and development expenses were EUR160.3 million compared to EUR110.6 million for the comparative prior-year period. The increase was mainly due to an increase in headcount leading to higher wages, benefits and social security expenses, as well as an increase in expenses for purchased research and development services, especially with respect to our BNT162 program.

In addition, from the date of acquisition, our new U.S.-based subsidiary BioNTech US Inc, contributed EUR5.3 million to our research and development expenses. General and administrative expenses were EUR18.8 million for the second quarter 2020 compared to EUR14.6 million for the second quarter 2019. For the six month ended June 30, 2020, total, general and administrative expenses were EUR34.6 million compared to EUR23.9 million for the comparative prior-year period. This increase was mainly influenced by higher expenses for purchase management consulting and legal services, as well as an increase in headcount leading to higher wages, benefits and total security expenses.

In addition, from the date of acquisition, our new U.S. based subsidiary BioNTech US Inc, contributed EUR1.6 million to our general and administrative expenses. Net loss was EUR88.3 million for the second quarter 2020 compared to EUR50.1 million for the second quarter 2019. For the six month ended June 30, 2020, total net loss was EUR141.7 million compared to EUR90.8 million for the comparative prior-year period.

Turning to the balance sheet on slide 26, BioNTech ended the second quarter 2020 with cash and cash equivalents of EUR573 million, or $641.6 million. Additionally, we raised EUR680.7 million or $762.2 million in gross proceeds from a private equity placement and our follow-on underwritten offering after the end of the second quarter. Considering these gross proceeds, the expected pro-forma cash and cash equivalents balance at June 30, 2020 amounts to EUR1.25 billion or $1.4 billion.

Further, we announced a debt financing of up to EUR100 million or $112 million from the European Investment Bank in June 2020. All financing transactions are subject to closing conditions that were not fulfilled before June 30, 2020 and did not have an accounting impact within the second quarter 2020. As a result of increased spending related to BNT162, we now expect net cash used in operating activities and for purchases of property and equipment to be between EUR450 million and EUR600 million for the full-year 2020.

We anticipate that existing cash and cash equivalents, the net proceeds from the recent underwritten offering and the expected net proceeds from the private investment announced in June 2020 will enable us to fund our operating expenses and capital requirements through at least the next 24 months. With that, I will return the call back to Ryan for concluding remarks.

Ryan Richardson {BIO 20337628 <GO>}

Thank you, Sierk. Slide 27 outlines the key milestones were focused on delivering as we look to the remainder of 2020. The first relates to our COVID-19 vaccine program, where the next major milestone is the Phase 2b/3 trial we are conducting with Pfizer. As Ozlem mentioned, we expect to be in a position to seek regulatory review as early as October 2020.

In the meantime, we expect to publish Phase 1 safety and immunogenicity data for BNT162b2 in the next few weeks. We also intend to publish preclinical data over the same time period. In addition, we anticipate three first-in-human data updates for our oncology programs over the course of the year, including for BNT114, BNT131 and our DuoBody program BNT311. Data from our BNT114 FixVac Phase 1 study in triple negative breast cancer has been accepted for an oral presentation at ESMO in mid-September.

The Phase 1 study is a three-arm trial as a monotherapy and in combination with iNeST evaluating safety and immunogenicity. The data to be presented will include a preliminary analysis of immune responses in TNBC patients treated with iNeST. For BNT131, our mRNA intratumoral immunotherapy program, partnered with Sanofi, we expect the data update for our Phase 1/2 trial in solid tumors in the second half of 2020. The study is a first-in-human, multicenter, open-label Phase 1 dose escalation and expansion trial to evaluate safety, pharmacokinetics, pharmacodynamics and antitumor activity of BNT131, both as a monotherapy and in combination with cemiplimab in patients with certain advanced solid tumors.

The data to be presented will include safety, tolerability and pharmacodynamic biomarker data. While updates for these programs will focus on safety and immunogenicity, we expect that our preliminary update for BNT311 our bi-specific antibody will also include top-line response data from our ongoing Phase 1/2 trial. And finally, we plan to initiate up to six additional studies from oncology pipeline over the remainder of 2020.

These include randomized Phase 2 trials for FixVac in melanoma and HPV16+ head and neck cancers, and for iNeST in adjuvant NSCLC and adjuvant CRC cancers. We also

anticipate initiating first-in-human trials for our cell therapy programs starting with our Claudin 6 CAR-T cell therapy, the first program to incorporate our CAR-T amplifying mRNA vaccine or CARVac approach.

And with that, I'll hand it back over to Ugur for concluding remarks.

Ugur Sahin {BIO 18869003 <GO>}

Thank you, Ryan. I'm proud of what we have accomplished over the first half of 2020 and believe a tremendous opportunity lies before us. We thank our shareholders and partners for their trust and support. Let us open up the call for questions now.

Questions And Answers

Operator

(Question And Answer)

Thank you. Ladies and gentlemen, we will now begin the question-and-answer session. (Operator Instructions). Your first question comes from the line of Tazeen Ahmad from Bank of America. Please ask your question.

Q - Analyst

Hi, good morning. This is Bill Maughan on for Tazeen. So two from me. First of all, how do you think about distributing the initial doses that are going to be manufactured later this year of the vaccine -- of the potential COVID vaccine assuming approval? So the initial doses manufactured later this year and early next year given that the first manufacturing batches won't immediately cover all supply agreements.

And then secondly when you have to repay the Pfizer upfront investment out of profit sharing, can you help quantify what Pfizer has already put up in terms of operating investment and what the pace of paying that back would be out of profit share and milestones? Thank you.

A - Ryan Richardson {BIO 20337628 <GO>}

Yes, I'll start with the first question. This is Ryan on the distribution side and then turn it over to Sierk to comment on the second. So, I think we're in the fortunate position to have considerable demand or interest in the vaccine as you can see from the supply deals that we've announced so far. Some of those deals do call for doses to be supplied in 2020, others in 2021. We've indicated that by '20 -- end of 2020 we'd expect to have up to 100 million doses and then expect to be able to increase our capacity pretty significantly as we head into 2021.

So I think we can't get into specifics at this point, but I think it's safe to say that we will -- already with the distribution agreements that we've announced, we feel confident that the

doses that we can produce, we'll be able to distribute across the countries that are included in those agreements.

I don't know, Sierk, do you want to comment on the second question?

A - Sierk Poetting {BIO 21288849 <GO>}

Yes, happy to. Actually so in Q2, this was the first reconciliation that we did with Pfizer and this quarter we reconciled $20 million as the total net cost on the BioNTech side, actually this was the 50% of cost-share for BioNTech in this quarter. So compared with the total program, still a small amount because it was ramping up in April and May and June so far. So, $20 million was recognized as cost so far as our share.

Q - Analyst

Okay. And I guess, how do you get to that $20 million given the large numbers that Pfizer has kind of put out in terms of what they are investing in their manufacturing?

A - Sierk Poetting {BIO 21288849 <GO>}

Yes. So, there's only a certain type of cost there. So, not everything is shared 50, 50, so investments are -- investments into capacity is everybody's own cost and what shared is basically the development cost and scale up. So this is shared, and this is -- the $20 million is our part of the share. And so far it's covered from our upfront that we'd received when signing the contract.

Q - Analyst

Okay. Thank you.

A - Sierk Poetting {BIO 21288849 <GO>}

Sure.

Operator

And your next question comes from the line of Cory Kasimov from JPMorgan. Please ask your question.

Q - Matthew Holt {BIO 18274461 <GO>}

Hey, guys. Thanks for taking my question. This is Matthew on for Cory. So I guess just wondering for BNT162 if you can talk a little bit about how you maintain the integrity of a Phase 3 blinded trial when a large proportion of the BNT162 patients are expected to get fevers and other systemic AEs and what your view is on whether this could impact the ultimate outcome of the trial?

A - Ugur Sahin {BIO 18869003 <GO>}

Yes. So thanks for the question. First of all, as we indicated in the press release when we announced the selection of BNT162b2, we indicated that b2 is significantly better tolerated than the b1. So actually only a little fraction of vaccinated individuals have fever and with regard to the other symptoms, you might have seen that even placebo vaccinated subjects have a number of background symptoms. So, we believe that we have a very good overall situation to avoid any type of bias negated by the understanding of the participant that he might or she might get the vaccine and not the placebo.

Q - Matthew Holt {BIO 18274461 <GO>}

Okay, great. And then just wondering if you can walk us through your assumptions or essentially what needs to happen for the Phase 3 program to get data and a potential regulatory filing in October. And just I guess maybe if you can help quantify how dependent this is on either enrollment or infection rates or what might be the key factor in the time line?

A - Ugur Sahin {BIO 18869003 <GO>}

Yes. So this is efficacy trial, that means at the end of the day, we are comparing the number of infected -- infections in the placebo whereas in the treatment group. We are online evaluating the blinded session, the safety data. The trial is proceeding very well. It's even recruiting faster than anticipated. And the overall concept is to wait until we have a given predefined number of events -- of infections event and then do a first evaluation, if there is significant difference between vaccine and placebo group.

The number -- the event number, so we will have several options, yes, to evaluate different event numbers and based on that -- based on the lower event numbers, you might be able to file already in October. If the lower event numbers do not support filing, we will have the opportunity to file four or six weeks later based, of course, on the assumption that the trial is positive.

Q - Matthew Holt {BIO 18274461 <GO>}

Great. Thanks for taking my questions.

A - Ugur Sahin {BIO 18869003 <GO>}

Yes, you're welcome.

Operator

Your next question comes from the line of Arlinda Lee from Canaccord. Please ask your question.

Q - Arlinda Lee {BIO 16422938 <GO>}

Thanks. Congrats on all the progress. I had a couple of questions on 162. One, can you provide an update on the enrollment of the pivotal trial? And two, I heard that some of the net costs for the trials have already -- you guided that, that was earlier in the development front. I'm wondering what you think that cost might be for the remainder of the year.

And then also on your oncology pipeline, I mean just more broadly, I guess, the rapidity and efficiency with which you guys have taken 162 into the clinic, I think highlights you guys' platform and I'm wondering what your appetite might be for additional collaborations, and if you've been getting inbound interest. Thank you.

A - Ugur Sahin {BIO 18869003 <GO>}

So maybe we start with the first question. I had difficulties to acoustically understand the second and the third question. So the recruitment, sort of my understanding is that, the first question was related how fast the recruitment happens for the pivotal trial. So we anticipate to recruit up to 30,000 subjects until mid of October and we are at the moment -- I can't tell you exact numbers. But trial is recruiting better than what was modeled. Yes. So we are on track and even ahead.

The second question, can you repeat the second question a little bit louder?

Q - Arlinda Lee {BIO 16422938 <GO>}

Yes. I'm just trying to, I guess, figure out on the cost sharing, how much you might accrue by year end.

A - Ugur Sahin {BIO 18869003 <GO>}

This is the question for Sierk.

A - Sierk Poetting {BIO 21288849 <GO>}

Yes, I can take this one. Yes so, as I mentioned before, so the net cost -- the net share in this quarter for BioNTech was $20 million and this was majorly driven by clinical costs, but also some preclinical research that was shared. So let's call it about a half or something was clinical cost, but remember May and June was only the Phase 1 trial, so basically patients were probably more expensive -- or sorry, subjects were more expensive, but also not as many. So I think, you can do the math and upgrade it to like it would be a lot more expensive in Q3 and with the Q3 numbers, we will also host like a better update, but it will be, yes, triple-digit million dollar amounts, I think.

A - Ryan Richardson {BIO 20337628 <GO>}

I mean, maybe just to add to that one point which is, we had previously guided, Arlinda, to EUR300 million of spend for the year and I think it's safe to say that we were tracking on that ex the Neon acquisition and the impact of COVID. So we've guided to EUR450 million to EUR600 million of net cash spend by the end of this year. So that delta there also gives you a sense for what the incremental amount could be.

Q - Arlinda Lee {BIO 16422938 <GO>}

Great. Thank you. And then I guess, the third question was, basically given you guys one or two kind of the platform, I'm kind of curious about whether you've gotten inbound interest and what your appetite might be for additional strategic collaborations.

A - Ugur Sahin {BIO 18869003 <GO>}

Maybe I can take the question. Yes, of course, this project of course validates our ability to respond quickly to challenges and opportunities. It validates our technology. It validates the safety of our approach and of course, it creates a lot of interest in future projects and we are in discussion with our partners for additional opportunities coming up in 2021.

Q - Arlinda Lee {BIO 16422938 <GO>}

Thank you.

Operator

Your next question comes from the line of Zhiqiang Shu from Berenberg. Please ask your question.

Q - Zhiqiang Shu {BIO 21945096 <GO>}

Hi, thank you. Good morning, everyone. Congrats on the progress. So, a few questions here on 162. I'd like to understand a little bit more on the old adults, the signals that you've seen in Phase 1 and 2. And maybe can you can qualitatively describe whether that's consistent with what people think the immune response there in this population is a lot lower than younger adults. And then whether the results from b2 would be -- b2 of again old adults would be included in the manuscript that you alluded in the few -- that will be available in a few weeks?

A - Ugur Sahin {BIO 18869003 <GO>}

Yes, so the first part of the question is older adults vaccine responses. So the size, I know, there are no publications yet on any group about vaccine responses in elderly adults, but as you, as everyone can guess and immune response in elderly adults is weaker, yes. And was likely for any vaccine platform, weaker. The reasons -- the reasons for that are twofold, it is the weaker innate immune response in elderly people and the second is the reduced number of naive T-cells and naive B-cells in elderly's. What we have observed is that, that a dose which is fully effective to induce a strong antibody and T-cell response in younger population is too low. In the elderly population, that's the reason why we increased the dose for our candidate b2 and with the increase of the dose, we are well in the range of a fully expective immune response or what is expected to be a fully effective immune response. And of course, yes, the data will be published with the next upcoming manuscript.

Q - Zhiqiang Shu {BIO 21945096 <GO>}

Okay. And then do you have a plan to publish any results from other variants on C2?

A - Ugur Sahin {BIO 18869003 <GO>}

From other candidates?

Q - Zhiqiang Shu {BIO 21945096 <GO>}

Yes. From other variants that were on Phase 1 and 2 study?

A - Ugur Sahin {BIO 18869003 <GO>}

Yes. We -- the other variants are in continued clinical evaluation with a somehow lower priorities. We expect to have a first publication related to another variant in October, and we will continue to share insights from this development program, which was not only just about selecting the first candidate but selecting the best candidate and also generating insights into the future generation of vaccines, which may come with lower doses, so where lower doses might result in the same type of immune response.

Q - Zhiqiang Shu {BIO 21945096 <GO>}

Great. That's helpful. And then finally just quickly touching on the oncology program BNT111. I remember there is an adjuvant cohort in the Phase 1 study. The results haven't been communicated. Is there anything that you have seen in that adjuvant melanoma cohort?

A - Ozlem Tureci {BIO 20629996 <GO>}

Thank you for that question. We are evaluating the adjuvant cohort as well and later this year, we will be able to report on that cohort as well.

Q - Zhiqiang Shu {BIO 21945096 <GO>}

Okay. Great. Thank you very much and congrats on the progress.

A - Ozlem Tureci {BIO 20629996 <GO>}

Thank you.

A - Ugur Sahin {BIO 18869003 <GO>}

Thank you.

Operator

Your next question comes from the line of Daina Graybosch from SVB. Please ask your question.

Q - Daina Graybosch {BIO 20659414 <GO>}

Thank you very much. Maybe I'll start with two on BNT162 and then after that come back for one on iNeST. So, on BNT162 two questions, one, there's been a lot made over differences in CD8 immunogenicity response between different companies and vaccines. And I wonder if you could comment on, if there's anything in the BNT162 mRNA construct or lipid nanoparticle that could be driving your relatively higher CD8 response versus some of the others?

And then the second question is, we've seen some of the CD8 and CD4 T-cell response data for our patients who have COVID-19. And then a lot of those publications there's a lot of response, I guess, on nucleocapsid especially for patients with certain HLA types. And I wonder what you think about your vaccines and others not including antigens for the nucleocapsid and whether that will be necessary in lifecycle management for full protection for old people.

A - Ugur Sahin {BIO 18869003 <GO>}

Okay. So thanks Daina for the questions. So first of all, yes, it's as, you know, our focus in messenger RNA vaccine development is optimizing not only antibody responses but particularly CD4 as well as CD8 responses. If you see the track record of the publications that we made in the last 10 years, we have included a number of independent optimizations to increase the translation of our messenger RNA in human dendritic cells. Which includes untranslated UTR regions, cap analogs and as well as the delivery of the vaccine. This CD8 response requires a direct expression of the antigen in dendritic cells.

So if you express the protein outside of the dendritic cells, the classical pathway for antigen presentation is uptake of the antigen by the exogenous presentation machinery of dendritic cells and presenting on class two which produced nice CD40 cell response. That's the reason why the spike on protein vaccines, and with vaccines which don't go into dendritic cells, you get CD40 cell responses, but the only way to get powerful CD8 responses is expression, strong expression with human dendritic cells, which we have proven for our platform and for the COVID-19 vaccine in detail, and I think this is the key differentiator for observing a stronger CD8 T-cell response.

The second part of the question was related -- what was the second question?

Q - Daina Graybosch {BIO 20659414 <GO>}

The nucleocapsid and whether there's some efficiency by not including that?

A - Ugur Sahin {BIO 18869003 <GO>}

Yes. I think if you ask the question what is the immunodominant antigen in an infection, this is not the same question with what antigen is particularly suitable to have a protective T-cell response. Yes, nucleoprotein is an immunodominant antigen, yes, but we know that the virus entry is mediated of course by the full virus and the spike protein is one of the key proteins in this virus and therefore having a protein and particularly with the supposed spike protein which is more than 1,200 amino acids and a large protein with 1,200 amino acids gives you multiple base of presentation of class 2 and class 1 epitopes on multiple MHC haplotypes. So, we believe that this spike protein is the near-perfect antigen.

We wanted clearly to avoid to add additional antigens into our vaccine because every additional antigen comes with an independent price, yes. and independent costs for potential diversification of the autoantibody repertoire. And therefore having a simple vaccine which is able to induce CD4 and CD8 T-cells in a broad population of people is

sufficient and we believe with this -- with the large spike protein we have an ideal candidate.

Q - Daina Graybosch {BIO 20659414 <GO>}

That's very helpful. And then on iNeST looking back at the data that was presented at AACR, one or two questions. I wonder if we should read anything to the biomarkers that there were a few TCM cells versus TEM cells? And also whether the number of sort of immunogenic neoantigens at around 2.6 is high enough. And sort of with both of those biomarkers if you're worried about them and if you're doing anything to optimize them as you go forward.

A - Ugur Sahin {BIO 18869003 <GO>}

Yes. And so the most important learnings from this bucket card is the feasibility of the approach for really multiple different indications for safety of the approach in different indications in combination also with atezo and the broad immunogenecity. The shortcomings of the part, of course, this is a bucket uncontrolled trial in patients with heavily pretreated and most of these patients had a progression-free survival time less than three months. So this is not an ideal population for vaccine. And therefore it's difficult to draw any conclusion with regard to potential clinical activity from this cohort. And this was the reason why we have already started in 2019, our randomized trial in melanoma, in certain melanoma which gives us with the PFS in the range of above nine months, gives us sufficient time to have a fully induced T-cells response, succeeded in the T-cells response.

And here, the key question is, if iNeST in combination with checkpoint locate in our first-line a highly mutated tumor type could induce an added benefit? So, this trial would help us to other indications with a similar type of profile. And the second learning not only from this iNeST type, but also from the melanoma trial that we had published in 2017 and followed up with updated data in 2020 is that tumors with lower tumor load might be the ideal setting for iNeST and that's the reason why we are going to start two clinical trials in ctDNA positive tumors, one is the non-small cell lung cancer program and the second one is the colorectal cancer trial.

And this is also based on a learning from the basket trial because in the colorectal cancer patient population that we have vaccinated, even though these were advanced patients, we observed really strong T-cell response, so that the number of mutation seems not be the limiting for application of iNeST in the population and that was encouraging enough to define it to two additional indications. So the next 12 months will be extremely informative for the iNeST project with data coming from the melanoma trial and with the randomized trials in lung cancer and colorectal cancer being active.

Q - Daina Graybosch {BIO 20659414 <GO>}

Great. Thank you very much.

A - Ugur Sahin {BIO 18869003 <GO>}

You're welcome.

Operator

Your next question comes from the line of Navin Jacob from UBS. Please ask your question.

Q - Navin Jacob {BIO 20931208 <GO>}

Hi. Yes. Thank you for taking my question. Can you hear me, okay?

A - Ozlem Tureci {BIO 20629996 <GO>}

Yes.

Q - Navin Jacob {BIO 20931208 <GO>}

Perfect. Thanks. Great. If I can -- I had quite a few, if I may start with the BNT162. Firstly, congrats on all the progress. Maybe, I could just on the trial design, I just was hoping for some clarity on some of the statistical powering assumptions. What is the trial powered for, for what size -- for what effect size and if you could provide any clarity on the number of events at the first interim look versus the second interim look, please and then I have some follow-up questions?

A - Ugur Sahin {BIO 18869003 <GO>}

So, these are maybe important questions. But at the moment, we are not able to share this information here. But what you can -- so what you can assume is that we have different interim readouts and these interim readouts of course come with different powers and with this different assumptions about the efficacy. So that's how the trial is in general structure, but I can't share the actual number.

Q - Navin Jacob {BIO 20931208 <GO>}

Okay. And then maybe on the regulatory requirement either based on an interim look and depending on the number of events, what is -- is there -- are there different requirements associated with say an interim look with 150 events versus 100 events? And attached to that, what is the regulatory requirement from a safety standpoint, a minimum follow-up of at least six months? If you were to file in October for example, based on an interim, would you have enough follow-up data as far as duration of the safety that would allow for emergency use authorization?

A - Ugur Sahin {BIO 18869003 <GO>}

Yes. So, the safety effect is addressed by two parameters. The one is the number of vaccinated subjects. Though, usually 3,000 subjects are sufficient to support a pandemic vaccine approval. The second is the follow-up time, and we are all aware that we have on the one side the need to get vaccine approved as fast as possible and make it available. For example, we are an emergency use authorization pathway, yes, and on the other side to continue to collect the safety data and that is exactly what is happening. So the subjects in this trial will be followed up for safety, safety parameters and we will get three months, say, to six months safety and we will continue also to monitor immune responses and the

stability of immune response in the subject to understand also the durability of the immune response.

Q - Navin Jacob {BIO 20931208 <GO>}

And what exactly does emergency use authorization mean in the context of the vaccine? Does that mean it can be used if you have the doses? Could that be used in a broad population or will it be only used in high-risk population such as patients in the front-line healthcare workers so on and so forth?

And then two quick other questions. So you mentioned long-term immunity. Wondering what gives you confidence or what are you seeing that should allow us to have some confidence in long-term immunity or memory function?

And then for on the Fosun partnership, I -- it looks like you're moving forward with 16b1 if I'm correct with Fosun and not 16b2. Maybe that's just -- is just earlier in where you're developing it in China, so maybe that's one. But if you could just clarify that, that would be appreciated.

A - Ugur Sahin {BIO 18869003 <GO>}

Okay, so let's start with the first question, who could benefit from the emergency use authorization. And of course, this is an issue of the governmental interest. So this is something where the U.S. government or the FDA had to decide for whom such a vaccine would be applicable. That's the same as in the Europe. It's a decision of every government to make the vaccine available and to be found to which population it should be made available.

The second question or the third question was about durability. So, we are collecting data with regard to durability of antibody response as well as evaluation of the durability of T-cell responses. So far, we have published data for up to 40 days -- 43 days and we will collect it for three months, six months, nine months, 12 months. We of course expect that the antibody titers will drop over time, that is what happens to antibody titers, which is vaccine in tandem. We have to see how fast this drop is and what is the baseline level where the drop stops, yes, and what kind of protection -- antibody-based protection still happens at this baseline level. So this is something which we will learn in the upcoming six months and continue to collect data.

I'm confident that having a vaccine which comes with a combined immune response, CD4, CD8, as well as antibody response based on the collaboration of this immune system arms, we will require lower amounts of each component since we will have a simplistic activity. But actually the community -- the whole scientific community and the industry has to learn what happens in the next two years, yes, how stable are these immune responses, what is required to protect from the infection.

If this is an issue -- if the drop of the immune response is an issue, I believe there's a messenger RNA vaccine we are in a good place to implement a booster immunization because this is one of the key strengths of messenger RNA vaccines, you can really use it

several times for boosting the immune response. It is not limited by any type of vector backbone immune response, which limits the activity of inducing and boosting antibody and T-cell response.

Q - Navin Jacob {BIO 20931208 <GO>}

Thank you so much and just maybe two very quick questions on FixVac. The T-cell data in the Nature publication certainly look interesting, but it is a plasma data. Wondering if what it looks like in the two micro environment, which, as you know, literature suggests there's better correlation with anti-tumor activity with tumor in T-cells -- or T-cells in tumor? So -- and then wondering also when we're going to see the next data set with a later cut-off point from this Phase 1?

A - Ugur Sahin {BIO 18869003 <GO>}

Yes. First of all, we have done in other studies, we analyzed tumor tissue and presence of T-cell receptors of -- vaccine-induced T-cell receptors, for example, in the iNeST trial but also for the FixVac and, yes, we confirm that T-cells that have been observed in the peripheral blood indeed infiltrate into the tumor and are detectable in the tumor.

So, this was not required to receive that in this special publication, which was more about the relationship between the strength and duration of the immune responses and the function of the immune response to cytotoxic assumption.

The next publication from this study will be sometime in 2021. I assume it's the second half of 2021 with regard to the population in this trial which is evaluated for relapse-free survival, so we had a patient population which -- who did not have tumors, metastatic tumor lesions but had surgery and afterwards received the therapy, and we will have relapse-free survival data here.

And actually the next upcoming publication would be the publication describing the Phase 2 data. And so we are -- as you know we are going to start a randomized Phase 3 study in melanoma FixVac end of the year and it will be a relatively small study which we'll record within the next 18 to 24 months. And I hope that this will be pivotal data required for registration of FixVac in second-line plus melanoma.

Q - Navin Jacob {BIO 20931208 <GO>}

Got it. I'm sorry. Sorry, the question on Fosun. Are you moving forward with 16b -- 162b1 with them or 16b2?

A - Ugur Sahin {BIO 18869003 <GO>}

No. Olzem, could you please answer?

A - Ozlem Tureci {BIO 20629996 <GO>}

Yes. Sure. We are moving further with b2 globally, also in China and with Fosun. The reason why the b1 part of the study of our testing in China has started basically at the

same time when we make the b2 decision, is that we think that it has value to also compare in the Chinese population, meaning, in other population these two candidates of mod-RNA platform and we are now preparing the b2 entry in China.

So the regulatory processes are the difference there. It's the more sequential approach, not the umbrella trial approach which works in that regulatory region. We think that generating class intrinsic data for mod-RNA as such and also benchmarking these to b1 and b2 mod-RNAs against each other in the Chinese population is of value for the entire program.

Q - Navin Jacob {BIO 20931208 <GO>}

That's very clear. Thank you very much for this call. Very helpful details and congrats on the progress.

A - Ozlem Tureci {BIO 20629996 <GO>}

Thank you.

Operator

In the interest of time, we ask participants to limit their questions to two please. Your next question comes from the line of Suzanne van Voorthuizen from Kempen. Please ask your question.

Q - Suzanne van Voorthuizen {BIO 19827693 <GO>}

Hi, good afternoon. I have a question on the COVID-19 vaccine. Looking back at the four different candidates that you went into Phase 1 with originally, I was just wondering for b1 and b2, these are mod-RNAs. It is our understanding that this format is more often used by BioNTech to de-immunize mRNA to make it especially useful for immune silent applications. So, can you elaborate a bit, are b1 and b2 also uridine modified? Or how are they modified to be more immunogenic?

A - Ugur Sahin {BIO 18869003 <GO>}

Yes. So, the rationale for starting with four different vaccine was on the one hand to evaluate our three different vaccine platforms. This is that modified messenger RNA platform which were now used for the candidate b1 and b2 and here b1 and b2 were selected based on the experience of the field in the past with MERS and the SARS, where both antigens had been evaluated but never benchmarked side by side.

A - Ozlem Tureci {BIO 20629996 <GO>}

(inaudible)

A - Ugur Sahin {BIO 18869003 <GO>}

Yes, with the RBD and the spike. And our study shows that both candidates are viable candidates with b2 having some advantage in this case.

For the second platform, with the uridine based platform, which comes with the potential advantage of a higher reactogenicity, and thereby stronger activity at low doses. We started to evaluate the RBD variant and generated some data and the data shows that we have immunogenicity. But the immunogenicity that not matched the immunogenicity that we have observed with the nucleus-modified mRNA.

And the second was -- the first candidate was the saRNA based candidate and here we have in the preclinical models, evaluated RBD as well as full spike and determined that the full spike for the self-amplifying mRNA is significantly better. So the only the full spike is currently evaluated and here we expect immunogenicity data since the really dose escalation study started with extremely low doses, yes, we expect the first relevant immunogenicity data in the time frame at the end of September and we will share that with the community. So the third amplified messenger RNA comes with the potential promise of having a potent vaccine candidate which comes with doses at lower in the low microgram range.

Q - Suzanne van Voorthuizen {BIO 19827693 <GO>}

Got it. And then maybe on the Phase 2, 3 trial, in terms of the primary endpoints, can you remind us of the bar that you have to achieve, was that a 50% reduction in infection rates? Do you need to hit both co-primary endpoints or one of the two to claim success?

A - Ugur Sahin {BIO 18869003 <GO>}

Yes. It's very simple. We stick to the guidance of the FDA and that's the lowest one.

Q - Suzanne van Voorthuizen {BIO 19827693 <GO>}

And are there co-primary endpoints, are they either/or, or are they and that you need to achieve to claim the success?

A - Ozlem Tureci {BIO 20629996 <GO>}

These are either/or.

Q - Suzanne van Voorthuizen {BIO 19827693 <GO>}

Okay, and maybe just one follow-up in this regard just to clarify for the filing. Is the primary endpoint data the hard requirements? Or maybe for an emergency use authorization? Will there be immunogenicity data analyzed with the interim analysis? Could it be that you can file on that if your primary endpoint data is trending in the right direction, for example, or is it a hard requirement?

A - Ugur Sahin {BIO 18869003 <GO>}

So, this is an ongoing discussion with the FDA, but I think the FDA was crystal clear when it announced in July the requirements for authorization and if this is still the case, then we would expect that use of the vaccine is only allowed when there are efficacy data around it.

Q - Suzanne van Voorthuizen {BIO 19827693 <GO>}

Got it. Alright. Thanks a lot.

A - Ugur Sahin {BIO 18869003 <GO>}

Yes.

Operator

Your final question comes from the line of Olga Smolentseva from Bryan, Garnier. Please ask your question.

Q - Olga Smolentseva {BIO 20860074 <GO>}

Good afternoon, everyone and thank you for taking my questions. Firstly on BNT162, considering that recent publications suggested that different mutations since spike protein could provide deeper immunogenicity. Could you maybe give us a little bit more color on the sort of optimization of the full spark antigen in b2? What kind of mutations in spike protein it includes?

A - Ugur Sahin {BIO 18869003 <GO>}

Yes, so we -- this is publicly used b2 stabilized -- prefusion stabilized mutation of the spike protein which has been described to use a stronger antibody response as compared to the virus-type protein.

Q - Olga Smolentseva {BIO 20860074 <GO>}

Okay. That's great. Thanks. And maybe just a little bit on BNT221. So how should we think about target population here in terms of differentiation with the planned potential pivotal BNT111 program?

A - Ozlem Tureci {BIO 20629996 <GO>}

Sorry, I didn't get that. Is this BNT111 -- sorry, it's on BNT221 --

A - Ryan Richardson {BIO 20337628 <GO>}

The Neon program.

Q - Olga Smolentseva {BIO 20860074 <GO>}

Yes. The Neon program.

A - Ozlem Tureci {BIO 20629996 <GO>}

Okay. The Neon program. Do you mean the adoptive T-cell therapy program which is just about to start?

Q - Olga Smolentseva {BIO 20860074 <GO>}

Yes, yes. I'm just interested in the target population here because it seems to overlap with BNT111 and I'm just thinking how -- yes, sorry.

A - Ugur Sahin {BIO 18869003 <GO>}

Yes. So the time which is going to start in Europe will be in relapsing melanoma -- metastatic melanoma patients and this is more or less a proof-of-concept study because the approach is really a legend. It is an approach of creating new antigen-specific T-cells directly from blood. So this is in principal a universal approach applicable to any type of tumor and the colleagues from BioNTech US have generated data also for other type of solid cancers. But melanoma is of course an excellent tumor type for first proof-of-concept study.

Q - Olga Smolentseva {BIO 20860074 <GO>}

Okay, great. Thank you. And many congratulations on all the progress.

A - Ugur Sahin {BIO 18869003 <GO>}

Yes. Thank you.

A - Ozlem Tureci {BIO 20629996 <GO>}

Thank you.

Operator

Thank you. I would now like to turn the conference back to Sylke Maas for closing remarks.

A - Sylke Maas {BIO 20912536 <GO>}

Thank you for joining today's call. We look forward to speaking to you in future. Stay safe. Bye-bye.

Operator

That does conclude our conference for today. Thank you for participating. You may all disconnect.

EXHIBIT 7

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use COMIRNATY safely and effectively. See full prescribing information for COMIRNATY.

COMIRNATY® (COVID-19 Vaccine, mRNA) suspension for injection, for intramuscular use
Initial U.S. Approval: 2021

---------- RECENT MAJOR CHANGES ----------

Indications and Usage (1)	7/2022
Dosage and Administration, Preparation for Administration (2.1)	7/2022

---------- INDICATIONS AND USAGE ----------

COMIRNATY is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- COMIRNATY supplied in multiple dose vials with purple caps and labels with purple borders MUST BE DILUTED before use. (2.1)
- For intramuscular injection only. (2.2)
- COMIRNATY is administered intramuscularly as a series of 2 doses (0.3 mL each) 3 weeks apart. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------

Suspension for injection. After preparation, a single dose is 0.3 mL. (3)

---------- CONTRAINDICATIONS ----------

Known history of a severe allergic reaction (e.g., anaphylaxis) to any component of COMIRNATY. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. (5.2)
- Syncope (fainting) may occur in association with administration of injectable vaccines, including COMIRNATY. Procedures should be in place to avoid injury from fainting. (5.4)

---------- ADVERSE REACTIONS ----------

- In clinical studies of participants 16 through 55 years of age, the most commonly reported adverse reactions (≥10%) were pain at the injection site (88.6%), fatigue (70.1%), headache (64.9%), muscle pain (45.5%), chills (41.5%), joint pain (27.5%), fever (17.8%), and injection site swelling (10.6%). (6.1)
- In clinical studies of participants 56 years of age and older, the most commonly reported adverse reactions (≥10%) were pain at the injection site (78.2%), fatigue (56.9%), headache, (45.9%), muscle pain (32.5%), chills (24.8%), joint pain (21.5%), injection site swelling (11.8%), fever (11.5%), and injection site redness (10.4%). (6.1)
- In clinical studies of adolescents 12 through 15 years of age, the most commonly reported adverse reactions (≥8%) were pain at the injection site (90.5%), fatigue (77.5%), headache (75.5%), chills (49.2%), muscle pain (42.2%), fever (24.3%), joint pain (20.2%), injection site swelling (9.2%), and injection site redness (8.6%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or VAERS at 1-800-822-7967 or http://vaers.hhs.gov.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 7/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

COMIRNATY is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Preparation for Administration

The storage, preparation, and administration information in this Prescribing Information apply to COMIRNATY for individuals 12 years of age and older supplied in multiple dose vials with purple caps and labels with purple borders, which **MUST BE DILUTED** before use.

COMIRNATY Multiple Dose Vial with a Purple Cap and Label with a Purple Border

Age Range	Dilution Information	Doses Per Vial After Dilution	Dose Volume
12 years and older	Dilute with 1.8 mL sterile 0.9% Sodium Chloride Injection, USP prior to use	6	0.3 mL

Dose Preparation

Each vial **MUST BE DILUTED** before administering the vaccine.

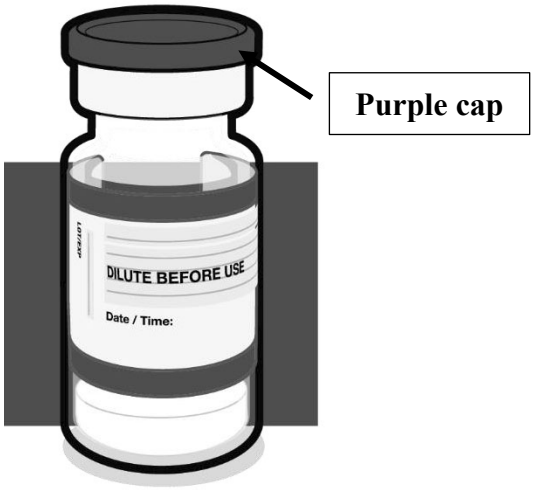
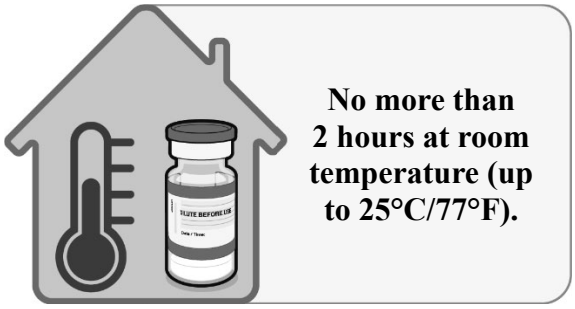
Prior to Dilution

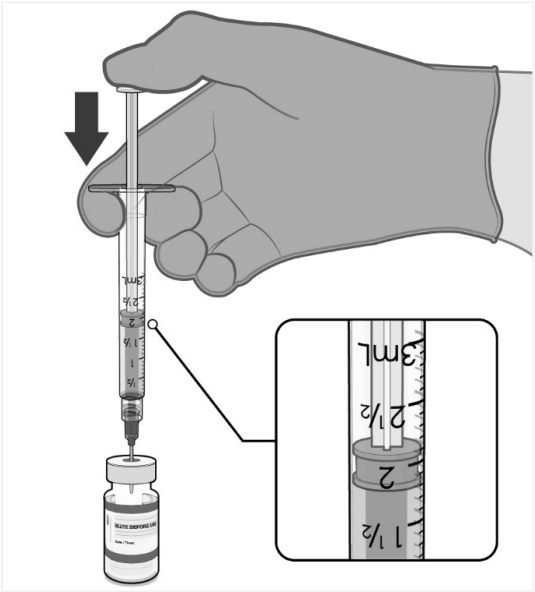
- COMIRNATY multiple dose vial with a purple cap and label with a purple border contains a volume of 0.45 mL, supplied as a frozen suspension that does not contain preservative.
- Each vial must be thawed before dilution.
- Vials may be thawed in the refrigerator [2ºC to 8ºC (35ºF to 46ºF)] or at room temperature [up to 25ºC (77ºF)] *[see How Supplied/Storage and Handling (16)]*.
- Refer to thawing instructions in the panels below.

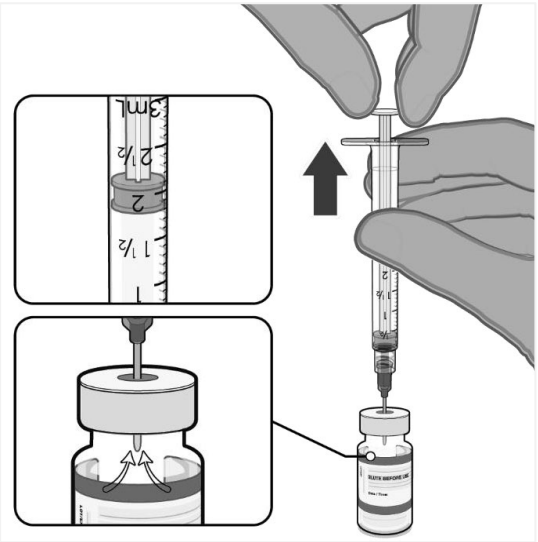
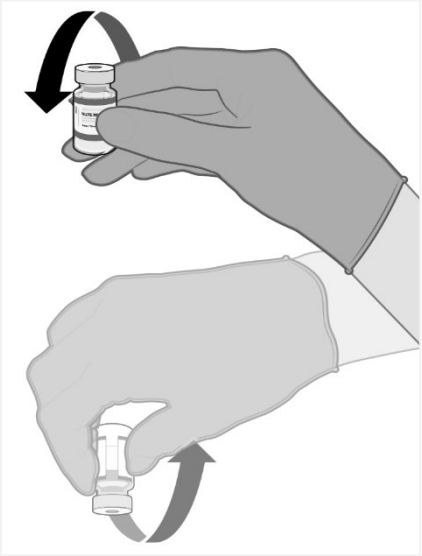
Dilution

- Dilute the vial contents using 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP to form COMIRNATY. Do not add more than 1.8 mL of diluent.
- ONLY use sterile 0.9% Sodium Chloride Injection, USP as the diluent. Do not use bacteriostatic 0.9% Sodium Chloride Injection or any other diluent.
- Vials of sterile 0.9% Sodium Chloride Injection, USP are provided but shipped separately. Use the provided diluent or another sterile 0.9% Sodium Chloride Injection, USP as the diluent.
    - Provided diluent vials are single-use only; discard after 1.8 mL is withdrawn.
    - If another sterile 0.9% Sodium Chloride Injection, USP is used as the diluent, discard after 1.8 mL is withdrawn.

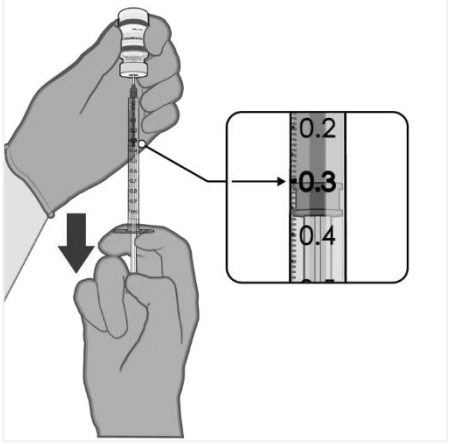
- Do not dilute more than 1 vial of COMIRNATY using the same diluent vial.
- After dilution, 1 vial of COMIRNATY contains 6 doses of 0.3 mL each.
- Refer to dilution and dose preparation instructions in the panels below.

Dilution and Preparation Instructions	
COMIRNATY Multiple Dose Vial with Purple Cap and Label with Purple Border – Vial Verification	
 ✓ **Purple plastic cap and label with purple border.**	• Verify that the vial of COMIRNATY has a purple plastic cap and a label with a purple border.
COMIRNATY Multiple Dose Vial with Purple Cap and Label with Purple Border – Thawing Prior to Dilution	
	• Thaw vial(s) of COMIRNATY before dilution either by: o Allowing vial(s) to thaw in the refrigerator [2ºC to 8ºC (35ºF to 46ºF)]. A carton of vials may take up to 3 hours to thaw, and thawed vials can be stored in the refrigerator for up to 1 month. o Allowing vial(s) to sit at room temperature [up to 25ºC (77ºF)] for 30 minutes. • Using either thawing method, vials must reach room temperature before dilution and must be diluted within 2 hours.

Dilution and Preparation Instructions	
 **Gently × 10**	• Before dilution invert vaccine vial gently 10 times. • Do not shake. • Inspect the liquid in the vial prior to dilution. The liquid is a white to off-white suspension and may contain white to off-white opaque amorphous particles. • Do not use if liquid is discolored or if other particles are observed.
COMIRNATY Multiple Dose Vial with Purple Cap and Label with Purple Border – Dilution	
 **Add 1.8 mL of sterile 0.9% sodium chloride injection, USP.**	• ONLY use sterile 0.9% Sodium Chloride Injection, USP as the diluent. • Withdraw 1.8 mL of diluent into a transfer syringe (21-gauge or narrower needle). • Add 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP into the vaccine vial.

Dilution and Preparation Instructions	
 **Pull back plunger to 1.8 mL to remove air from vial.**	• Equalize vial pressure before removing the needle from the vaccine vial by withdrawing 1.8 mL air into the empty diluent syringe.
 **Gently × 10**	• Gently invert the vial containing COMIRNATY 10 times to mix. • Do not shake. • Inspect the vaccine in the vial. • The vaccine will be an off-white suspension. Do not use if vaccine is discolored or contains particulate matter.

<table>
<tr><th colspan="2">Dilution and Preparation Instructions</th></tr>
<tr><td> 

Record the date and time of dilution.
Use within 6 hours after dilution.</td><td>• Record the date and time of dilution on the COMIRNATY vial label.
• Store between 2°C to 25°C (35°F to 77°F).
• Discard any unused vaccine 6 hours after dilution.</td></tr>
<tr><th colspan="2">COMIRNATY Multiple Dose Vial with Purple Cap and Label with Purple Border – Preparation of Individual 0.3 mL Doses</th></tr>
<tr><td> 

Withdraw 0.3 mL dose of vaccine.</td><td>• Withdraw 0.3 mL of COMIRNATY preferentially using low dead-volume syringes and/or needles.
• Each dose must contain 0.3 mL of vaccine.
• If the amount of vaccine remaining in a single vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
• Administer immediately.</td></tr>
</table>

2.2 Administration Information

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The vaccine will be an off-white suspension. Do not administer if vaccine is discolored or contains particulate matter.

Administer a single 0.3 mL dose of COMIRNATY intramuscularly.

After dilution, vials of COMIRNATY with purple caps and labels with purple borders contain 6 doses of 0.3 mL of vaccine. Low dead-volume syringes and/or needles can be used to extract 6 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract 6 doses from a single vial. Irrespective of the type of syringe and needle,

- each dose must contain 0.3 mL of vaccine.
- if the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.

- do not pool excess vaccine from multiple vials.

2.3 Vaccination Schedule

COMIRNATY is administered intramuscularly as a series of 2 doses (0.3 mL each) 3 weeks apart.

There are no data available on the interchangeability of COMIRNATY with COVID-19 vaccines from other manufacturers to complete the vaccination series. Individuals who have received 1 dose of COMIRNATY should receive a second dose of COMIRNATY to complete the vaccination series.

3 DOSAGE FORMS AND STRENGTHS

COMIRNATY is a suspension for injection. After preparation, each dose of COMIRNATY supplied in vials with purple caps and labels with purple borders is 0.3 mL.

4 CONTRAINDICATIONS

Do not administer COMIRNATY to individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the COMIRNATY *[see Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

Appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of COMIRNATY.

5.2 Myocarditis and Pericarditis

Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk is higher among males under 40 years of age than among females and older males. The observed risk is highest in males 12 through 17 years of age. Although some cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae. The CDC has published considerations related to myocarditis and pericarditis after vaccination, including for vaccination of individuals with a history of myocarditis or pericarditis (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html).

5.3 Syncope

Syncope (fainting) may occur in association with administration of injectable vaccines, including COMIRNATY. Procedures should be in place to avoid injury from fainting.

5.4 Altered Immunocompetence

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the COMIRNATY.

5.5 Limitation of Effectiveness

COMIRNATY may not protect all vaccine recipients.

6 ADVERSE REACTIONS

In clinical studies, the most commonly reported (≥10%) adverse reactions in participants 16 through 55 years of age following any dose were pain at the injection site (88.6%), fatigue (70.1%), headache (64.9%), muscle pain (45.5%), chills (41.5%), joint pain (27.5%), fever (17.8%), and injection site swelling (10.6%).

In clinical studies, the most commonly reported (≥10%) adverse reactions in participants 56 years of age and older following any dose were pain at the injection site (78.2%), fatigue (56.9%), headache, (45.9%), muscle pain (32.5%), chills (24.8%), joint pain (21.5%), injection site swelling (11.8%), fever (11.5%), and injection site redness (10.4%).

In a clinical study, the most commonly reported (≥8%) adverse reactions in adolescents 12 through 15 years of age following any dose were pain at the injection site (90.5%), fatigue (77.5%), headache (75.5%), chills (49.2%), muscle pain (42.2%), fever (24.3%), joint pain (20.2%), injection site swelling (9.2%), and injection site redness (8.6%).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

The safety of COMIRNATY was evaluated in participants 12 years of age and older in 2 clinical studies conducted in Germany (Study 1), United States, Argentina, Brazil, Turkey, South Africa, and Germany (Study 2). Study BNT162-01 (Study 1) was a Phase 1/2, 2-part, dose-escalation trial that enrolled 60 participants, 18 through 55 years of age and 36 participants, 56 through 85 years of age. Study C4591001 (Study 2) is a Phase 1/2/3 multicenter, multinational, randomized, saline placebo-controlled, double-blinded (Phase 2/3), dose-finding, vaccine candidate-selection and efficacy study that has enrolled approximately 46,000 participants 12 years of age or older. Of these, approximately 44,047 participants (22,026 COMIRNATY; 22,021 placebo) in Phase 2/3 are 16 years of age or older (including 378 and 376 participants 16 through 17 years of age in the COMIRNATY and placebo groups, respectively) and 2,260 adolescents are 12 through 15 years of age (1,131 and 1,129 in the COMIRNATY and placebo groups, respectively). Upon issuance of the Emergency Use Authorization for COMIRNATY, participants were unblinded to offer placebo participants COMIRNATY. Participants were unblinded in a phased manner over a period of months to offer placebo participants COMIRNATY. Study 2 also included 200 participants with confirmed stable human immunodeficiency virus (HIV) infection; HIV-positive participants are included in safety population disposition but are summarized separately in safety analyses. Confirmed stable HIV infection was defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

In Study 2, all participants 12 through 15 years of age, and 16 years and older in the reactogenicity subset were monitored for solicited local and systemic reactions and use of antipyretic medication after each vaccination in an electronic diary. Participants are being monitored for unsolicited adverse events, including serious adverse events, throughout the study [from Dose 1 through 1 month (all unsolicited adverse events) or 6 months (serious adverse events) after the last vaccination]. Tables 1 through 6 present the frequency and severity of solicited local and systemic reactions, respectively, within 7 days following each dose of COMIRNATY and placebo.

Participants 16 Years of Age and Older

At the time of the analysis of the ongoing Study 2 with a data cutoff of March 13, 2021, there were 25,651 (58.2%) participants (13,031 COMIRNATY and 12,620 placebo) 16 years of age and older followed for ≥4 months after the second dose.

Demographic characteristics in Study 2 were generally similar with regard to age, gender, race, and ethnicity among participants who received COMIRNATY and those who received placebo. Overall, among the total participants who received either COMIRNATY or placebo, 50.9% were male, 49.1% were female, 79.3% were 16 through 64 years of age, 20.7% were 65 years of age and older, 82.0% were White, 9.6% were Black or African American, 25.9% were Hispanic/Latino, 4.3% were Asian, and 1.0% were American Indian or Alaska Native.

Local and Systemic Adverse Reactions Solicited in the Study 2
In participants 16 through 55 years of age after receiving Dose 2, the mean duration of pain at the injection site was 2.5 days (range 1 to 70 days), for redness 2.2 days (range 1 to 9 days), and for swelling 2.1 days (range 1 to 8 days) for participants in the COMIRNATY group. In participants 56 years of age and older after receiving Dose 2, the mean duration of pain at the injection site was 2.4 days (range 1 to 36 days), for redness 3.0 days (range 1 to 34 days), and for swelling 2.6 days (range 1 to 34 days) for participants in the COMIRNATY group.

Table 1: Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 16 Through 55 Years of Age – Reactogenicity Subset of the Safety Population*

	COMIRNATY Dose 1 N[a]=2899 n[b] (%)	**Placebo Dose 1 N[a]=2908 n[b] (%)**	**COMIRNATY Dose 2 N[a]=2682 n[b] (%)**	**Placebo Dose 2 N[a]=2684 n[b] (%)**
Redness[c]				
Any (>2.0 cm)	156 (5.4)	28 (1.0)	151 (5.6)	18 (0.7)
Mild	113 (3.9)	19 (0.7)	90 (3.4)	12 (0.4)
Moderate	36 (1.2)	6 (0.2)	50 (1.9)	6 (0.2)
Severe	7 (0.2)	3 (0.1)	11 (0.4)	0
Swelling[c]				
Any (>2.0 cm)	184 (6.3)	16 (0.6)	183 (6.8)	5 (0.2)
Mild	124 (4.3)	6 (0.2)	110 (4.1)	3 (0.1)
Moderate	54 (1.9)	8 (0.3)	66 (2.5)	2 (0.1)
Severe	6 (0.2)	2 (0.1)	7 (0.3)	0

	COMIRNATY Dose 1 N[a]=2899 n[b] (%)	Placebo Dose 1 N[a]=2908 n[b] (%)	COMIRNATY Dose 2 N[a]=2682 n[b] (%)	Placebo Dose 2 N[a]=2684 n[b] (%)
Pain at the injection site[d]				
Any	2426 (83.7)	414 (14.2)	2101 (78.3)	312 (11.6)
Mild	1464 (50.5)	391 (13.4)	1274 (47.5)	284 (10.6)
Moderate	923 (31.8)	20 (0.7)	788 (29.4)	28 (1.0)
Severe	39 (1.3)	3 (0.1)	39 (1.5)	0

Notes: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
No Grade 4 solicited local reactions were reported in participants 16 through 55 years of age.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention. Participants with chronic, stable HIV infection were excluded.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose. The N for each reaction was the same, therefore, this information was included in the column header.

b. n = Number of participants with the specified reaction.

c. Mild: >2.0 to ≤5.0 cm; Moderate: >5.0 to ≤10.0 cm; Severe: >10.0 cm.

d. Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

Table 2: Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 16 Through 55 Years of Age – Reactogenicity Subset of the Safety Population*

	COMIRNATY Dose 1 N[a]=2899 n[b] (%)	Placebo Dose 1 N[a]=2908 n[b] (%)	COMIRNATY Dose 2 N[a]=2682 n[b] (%)	Placebo Dose 2 N[a]=2684 n[b] (%)
Fever				
≥38.0°C	119 (4.1)	25 (0.9)	440 (16.4)	11 (0.4)
≥38.0°C to 38.4°C	86 (3.0)	16 (0.6)	254 (9.5)	5 (0.2)
>38.4°C to 38.9°C	25 (0.9)	5 (0.2)	146 (5.4)	4 (0.1)
>38.9°C to 40.0°C	8 (0.3)	4 (0.1)	39 (1.5)	2 (0.1)
>40.0°C	0	0	1 (0.0)	0
Fatigue[c]				
Any	1431 (49.4)	960 (33.0)	1649 (61.5)	614 (22.9)
Mild	760 (26.2)	570 (19.6)	558 (20.8)	317 (11.8)
Moderate	630 (21.7)	372 (12.8)	949 (35.4)	283 (10.5)
Severe	41 (1.4)	18 (0.6)	142 (5.3)	14 (0.5)
Headache[c]				
Any	1262 (43.5)	975 (33.5)	1448 (54.0)	652 (24.3)
Mild	785 (27.1)	633 (21.8)	699 (26.1)	404 (15.1)
Moderate	444 (15.3)	318 (10.9)	658 (24.5)	230 (8.6)
Severe	33 (1.1)	24 (0.8)	91 (3.4)	18 (0.7)
Chills[c]				
Any	479 (16.5)	199 (6.8)	1015 (37.8)	114 (4.2)
Mild	338 (11.7)	148 (5.1)	477 (17.8)	89 (3.3)
Moderate	126 (4.3)	49 (1.7)	469 (17.5)	23 (0.9)
Severe	15 (0.5)	2 (0.1)	69 (2.6)	2 (0.1)

	COMIRNATY Dose 1 N[a]=2899 n[b] (%)	Placebo Dose 1 N[a]=2908 n[b] (%)	COMIRNATY Dose 2 N[a]=2682 n[b] (%)	Placebo Dose 2 N[a]=2684 n[b] (%)
Vomiting[d]				
Any	34 (1.2)	36 (1.2)	58 (2.2)	30 (1.1)
Mild	29 (1.0)	30 (1.0)	42 (1.6)	20 (0.7)
Moderate	5 (0.2)	5 (0.2)	12 (0.4)	10 (0.4)
Severe	0	1 (0.0)	4 (0.1)	0
Diarrhea[e]				
Any	309 (10.7)	323 (11.1)	269 (10.0)	205 (7.6)
Mild	251 (8.7)	264 (9.1)	219 (8.2)	169 (6.3)
Moderate	55 (1.9)	58 (2.0)	44 (1.6)	35 (1.3)
Severe	3 (0.1)	1 (0.0)	6 (0.2)	1 (0.0)
New or worsened muscle pain[c]				
Any	664 (22.9)	329 (11.3)	1055 (39.3)	237 (8.8)
Mild	353 (12.2)	231 (7.9)	441 (16.4)	150 (5.6)
Moderate	296 (10.2)	96 (3.3)	552 (20.6)	84 (3.1)
Severe	15 (0.5)	2 (0.1)	62 (2.3)	3 (0.1)
New or worsened joint pain[c]				
Any	342 (11.8)	168 (5.8)	638 (23.8)	147 (5.5)
Mild	200 (6.9)	112 (3.9)	291 (10.9)	82 (3.1)
Moderate	137 (4.7)	55 (1.9)	320 (11.9)	61 (2.3)
Severe	5 (0.2)	1 (0.0)	27 (1.0)	4 (0.1)
Use of antipyretic or pain medication[f]	805 (27.8)	398 (13.7)	1213 (45.2)	320 (11.9)

Notes: Reactions and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.

No Grade 4 solicited systemic reactions were reported in participants 16 through 55 years of age.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention. Participants with chronic, stable HIV infection were excluded.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose. The N for each reaction or use of antipyretic or pain medication was the same, therefore, this information was included in the column header.

b. n = Number of participants with the specified reaction.

c. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.

d. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.

e. Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.

f. Severity was not collected for use of antipyretic or pain medication.

Table 3: Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 56 Years of Age and Older – Reactogenicity Subset of the Safety Population*

	COMIRNATY Dose 1 N[a]=2008 n[b] (%)	Placebo Dose 1 N[a]=1989 n[b] (%)	COMIRNATY Dose 2 N[a]=1860 n[b] (%)	Placebo Dose 2 N[a]=1833 n[b] (%)
Redness[c]				
Any (>2.0 cm)	106 (5.3)	20 (1.0)	133 (7.2)	14 (0.8)
Mild	71 (3.5)	13 (0.7)	65 (3.5)	10 (0.5)
Moderate	30 (1.5)	5 (0.3)	58 (3.1)	3 (0.2)
Severe	5 (0.2)	2 (0.1)	10 (0.5)	1 (0.1)

	COMIRNATY Dose 1 N[a]=2008 n[b] (%)	Placebo Dose 1 N[a]=1989 n[b] (%)	COMIRNATY Dose 2 N[a]=1860 n[b] (%)	Placebo Dose 2 N[a]=1833 n[b] (%)
Swelling[c]				
Any (>2.0 cm)	141 (7.0)	23 (1.2)	145 (7.8)	13 (0.7)
Mild	87 (4.3)	11 (0.6)	80 (4.3)	5 (0.3)
Moderate	52 (2.6)	12 (0.6)	61 (3.3)	7 (0.4)
Severe	2 (0.1)	0	4 (0.2)	1 (0.1)
Pain at the injection site[d]				
Any (>2.0 cm)	1408 (70.1)	185 (9.3)	1230 (66.1)	143 (7.8)
Mild	1108 (55.2)	177 (8.9)	873 (46.9)	138 (7.5)
Moderate	296 (14.7)	8 (0.4)	347 (18.7)	5 (0.3)
Severe	4 (0.2)	0	10 (0.5)	0

Notes: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
No Grade 4 solicited local reactions were reported in participants 56 years of age and older.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention. Participants with chronic, stable HIV infection were excluded.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose. The N for each reaction was the same, therefore, the information was included in the column header.

b. n = Number of participants with the specified reaction.

c. Mild: >2.0 to ≤5.0 cm; Moderate: >5.0 to ≤10.0 cm; Severe: >10.0 cm.

d. Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

Table 4: Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 56 Years of Age and Older – Reactogenicity Subset of the Safety Population*

	COMIRNATY Dose 1 N[a]=2008 n[b] (%)	Placebo Dose 1 N[a]=1989 n[b] (%)	COMIRNATY Dose 2 N[a]=1860 n[b] (%)	Placebo Dose 2 N[a]=1833 n[b] (%)
Fever				
≥38.0°C	26 (1.3)	8 (0.4)	219 (11.8)	4 (0.2)
≥38.0°C to 38.4°C	23 (1.1)	3 (0.2)	158 (8.5)	2 (0.1)
>38.4°C to 38.9°C	2 (0.1)	3 (0.2)	54 (2.9)	1 (0.1)
>38.9°C to 40.0°C	1 (0.0)	2 (0.1)	7 (0.4)	1 (0.1)
>40.0°C	0	0	0	0
Fatigue[c]				
Any	677 (33.7)	447 (22.5)	949 (51.0)	306 (16.7)
Mild	415 (20.7)	281 (14.1)	391 (21.0)	183 (10.0)
Moderate	259 (12.9)	163 (8.2)	497 (26.7)	121 (6.6)
Severe	3 (0.1)	3 (0.2)	60 (3.2)	2 (0.1)
Grade 4	0	0	1 (0.1)	0
Headache[c]				
Any	503 (25.0)	363 (18.3)	733 (39.4)	259 (14.1)
Mild	381 (19.0)	267 (13.4)	464 (24.9)	189 (10.3)
Moderate	120 (6.0)	93 (4.7)	256 (13.8)	65 (3.5)
Severe	2 (0.1)	3 (0.2)	13 (0.7)	5 (0.3)

	COMIRNATY Dose 1 N[a]=2008 n[b] (%)	Placebo Dose 1 N[a]=1989 n[b] (%)	COMIRNATY Dose 2 N[a]=1860 n[b] (%)	Placebo Dose 2 N[a]=1833 n[b] (%)
Chills[c]				
Any	130 (6.5)	69 (3.5)	435 (23.4)	57 (3.1)
Mild	102 (5.1)	49 (2.5)	229 (12.3)	45 (2.5)
Moderate	28 (1.4)	19 (1.0)	185 (9.9)	12 (0.7)
Severe	0	1 (0.1)	21 (1.1)	0
Vomiting[d]				
Any	10 (0.5)	9 (0.5)	13 (0.7)	5 (0.3)
Mild	9 (0.4)	9 (0.5)	10 (0.5)	5 (0.3)
Moderate	1 (0.0)	0	1 (0.1)	0
Severe	0	0	2 (0.1)	0
Diarrhea[e]				
Any	168 (8.4)	130 (6.5)	152 (8.2)	102 (5.6)
Mild	137 (6.8)	109 (5.5)	125 (6.7)	76 (4.1)
Moderate	27 (1.3)	20 (1.0)	25 (1.3)	22 (1.2)
Severe	4 (0.2)	1 (0.1)	2 (0.1)	4 (0.2)
New or worsened muscle pain[c]				
Any	274 (13.6)	165 (8.3)	537 (28.9)	99 (5.4)
Mild	183 (9.1)	111 (5.6)	229 (12.3)	65 (3.5)
Moderate	90 (4.5)	51 (2.6)	288 (15.5)	33 (1.8)
Severe	1 (0.0)	3 (0.2)	20 (1.1)	1 (0.1)
New or worsened joint pain[c]				
Any	175 (8.7)	124 (6.2)	353 (19.0)	72 (3.9)
Mild	119 (5.9)	78 (3.9)	183 (9.8)	44 (2.4)
Moderate	53 (2.6)	45 (2.3)	161 (8.7)	27 (1.5)
Severe	3 (0.1)	1 (0.1)	9 (0.5)	1 (0.1)
Use of antipyretic or pain medication[f]	382 (19.0)	224 (11.3)	688 (37.0)	170 (9.3)

Notes: Reactions and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.

The only Grade 4 solicited systemic reaction reported in participants 56 years of age and older was fatigue.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention. Participants with chronic, stable HIV infection were excluded.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose. N for each reaction or use of antipyretic or pain medication was the same, therefore was included in the column header.

b. n = Number of participants with the specified reaction.

c. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity; Grade 4 reactions were defined in the clinical study protocol as emergency room visit or hospitalization for severe fatigue, severe headache, severe chills, severe muscle pain, or severe joint pain.

d. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration; Grade 4 emergency visit or hospitalization for severe vomiting.

e. Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours; Grade 4: emergency room or hospitalization for severe diarrhea.

f. Severity was not collected for use of antipyretic or pain medication.

In participants with chronic, stable HIV infection the frequencies of solicited local and systemic adverse reactions were similar to or lower than those observed for all participants 16 years of age and older.

Unsolicited Adverse Events

Overall, 11,253 (51.1%) participants in the COMIRNATY group and 11,316 (51.4%) participants in the placebo group had follow-up time between ≥4 months to <6 months after Dose 2 in the blinded placebo-controlled follow-up period with an additional 1,778 (8.1%) and 1,304 (5.9%) with ≥6 months of blinded follow-up time in the COMIRNATY and placebo groups, respectively.

A total of 12,006 (54.5%) participants originally randomized to COMIRNATY had ≥6 months total (blinded and unblinded) follow-up after Dose 2.

In an analysis of all unsolicited adverse events reported following any dose, through 1 month after Dose 2, in participants 16 years of age and older (N=43,847; 21,926 COMIRNATY group vs. 21,921 placebo group), those assessed as adverse reactions not already captured by solicited local and systemic reactions were nausea (274 vs. 87), malaise (130 vs. 22), lymphadenopathy (83 vs. 7), asthenia (76 vs. 25), decreased appetite (39 vs. 9), hyperhidrosis (31 vs. 9), lethargy (25 vs. 6), and night sweats (17 vs. 3).

In analyses of all unsolicited adverse events in Study 2 from Dose 1 up to the participant unblinding date, 58.2% of study participants had at least 4 months of follow-up after Dose 2. Among participants 16 through 55 years of age who received at least 1 dose of study vaccine, 12,995 of whom received COMIRNATY and 13,026 of whom received placebo, unsolicited adverse events were reported by 4,396 (33.8%) participants in the COMIRNATY group and 2,136 (16.4%) participants in the placebo group. In a similar analysis in participants 56 years of age and older that included 8,931 COMIRNATY recipients and 8,895 placebo recipients, unsolicited adverse events were reported by 2,551 (28.6%) participants in the COMIRNATY group and 1,432 (16.1%) participants in the placebo group. Among participants with confirmed stable HIV infection that included 100 COMIRNATY recipients and 100 placebo recipients, unsolicited adverse events were reported by 29 (29%) participants in the COMIRNATY group and 15 (15%) participants in the placebo group. The higher frequency of reported unsolicited adverse events among COMIRNATY recipients compared to placebo recipients was primarily attributed to events that are consistent with adverse reactions solicited among participants in the reactogenicity subset (Table 3 and Table 4).

Throughout the placebo-controlled safety follow-up period, Bell's palsy (facial paralysis) was reported by 4 participants in the COMIRNATY group and 2 participants in the placebo group. Onset of facial paralysis was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. In the placebo group the onset of facial paralysis was Day 32 and Day 102. Currently available information is insufficient to determine a causal relationship with the vaccine. In the analysis of blinded, placebo-controlled follow-up, there were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic or neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to COMIRNATY. In the analysis of unblinded follow-up, there were no notable patterns of specific categories of non-serious adverse events that would suggest a causal relationship to COMIRNATY.

Serious Adverse Events

In Study 2, among participants 16 through 55 years of age who had received at least 1 dose of vaccine or placebo (COMIRNATY =12,995; placebo = 13,026), serious adverse events from Dose 1 up to the participant unblinding date in ongoing follow-up were reported by 103 (0.8%) COMIRNATY recipients and 117 (0.9%) placebo recipients. In a similar analysis, in participants 56 years of age and older (COMIRNATY = 8,931; placebo = 8,895), serious adverse events were reported by 165 (1.8%) COMIRNATY recipients and 151 (1.7%) placebo recipients who received at least 1 dose of COMIRNATY or placebo, respectively. In these analyses, 58.2% of study participants had at least 4 months of follow-up after Dose 2. Among participants with confirmed

stable HIV infection serious adverse events from Dose 1 up to the participant unblinding date in ongoing follow-up were reported by 2 (2%) COMIRNATY recipients and 2 (2%) placebo recipients.

In the analysis of blinded, placebo-controlled follow-up, there were no notable patterns between treatment groups for specific categories of serious adverse events (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to COMIRNATY. In the analysis of unblinded follow-up, there were no notable patterns of specific categories of serious adverse events that would suggest a causal relationship to COMIRNATY.

Adolescents 12 Through 15 Years of Age

In Study 2, 2,260 adolescents (1,131 COMIRNATY; 1,129 placebo) were 12 through 15 years of age. At the time of the analysis of the ongoing Study 2 with a data cutoff of September 2, 2021, there were 1,559 (69.0%) adolescents (786 COMIRNATY and 773 placebo) 12 through 15 years of age followed for ≥4 months after the second dose. The safety evaluation in Study 2 is ongoing.

Demographic characteristics in Study 2 were generally similar with regard to age, gender, race, and ethnicity among adolescents who received COMIRNATY and those who received placebo. Overall, among the adolescents who received COMIRNATY, 50.1% were male and 49.9% were female, 85.8% were White, 4.6% were Black or African American, 11.7% were Hispanic/Latino, 6.4% were Asian, and 0.4% were American Indian/Alaska Native.

Local and Systemic Adverse Reactions Solicited in Study 2

In adolescents 12 through 15 years of age after receiving Dose 2, the mean duration of pain at the injection site was 2.5 days (range 1 to 11 days), for redness 1.8 days (range 1 to 5 days), and for swelling 1.6 days (range 1 to 5 days) in the COMIRNATY group.

Table 5: Study 2 – Frequency and Percentages of Adolescents With Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Adolescents 12 Through 15 Years of Age – Safety Population*

	COMIRNATY Dose 1 N[a]=1127 n[b] (%)	**Placebo Dose 1 N[a]=1127 n[b] (%)**	**COMIRNATY Dose 2 N[a]=1097 n[b] (%)**	**Placebo Dose 2 N[a]=1078 n[b] (%)**
Redness[c]				
Any (>2 cm)	65 (5.8)	12 (1.1)	55 (5.0)	10 (0.9)
Mild	44 (3.9)	11 (1.0)	29 (2.6)	8 (0.7)
Moderate	20 (1.8)	1 (0.1)	26 (2.4)	2 (0.2)
Severe	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Swelling[c]				
Any (>2 cm)	78 (6.9)	11 (1.0)	54 (4.9)	6 (0.6)
Mild	55 (4.9)	9 (0.8)	36 (3.3)	4 (0.4)
Moderate	23 (2.0)	2 (0.2)	18 (1.6)	2 (0.2)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	COMIRNATY Dose 1 N[a]=1127 n[b] (%)	Placebo Dose 1 N[a]=1127 n[b] (%)	COMIRNATY Dose 2 N[a]=1097 n[b] (%)	Placebo Dose 2 N[a]=1078 n[b] (%)
Pain at the injection site[d]				
Any	971 (86.2)	263 (23.3)	866 (78.9)	193 (17.9)
Mild	467 (41.4)	227 (20.1)	466 (42.5)	164 (15.2)
Moderate	493 (43.7)	36 (3.2)	393 (35.8)	29 (2.7)
Severe	11 (1.0)	0 (0.0)	7 (0.6)	0 (0.0)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
b. n = Number of participants with the specified reaction.
c. Mild: >2.0 to ≤5.0 cm; Moderate: >5.0 to ≤10.0 cm; Severe: >10.0 cm.
d. Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

Table 6: Study 2 – Frequency and Percentages of Adolescents with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – Adolescents 12 Through 15 Years of Age – Safety Population*

	COMIRNATY Dose 1 N[a]=1127 n[b] (%)	Placebo Dose 1 N[a]=1127 n[b] (%)	COMIRNATY Dose 2 N[a]=1097 n[b] (%)	Placebo Dose 2 N[a]=1078 n[b] (%)
Fever				
≥38.0°C	114 (10.1)	12 (1.1)	215 (19.6)	7 (0.6)
≥38.0°C to 38.4°C	74 (6.6)	8 (0.7)	107 (9.8)	5 (0.5)
>38.4°C to 38.9°C	29 (2.6)	2 (0.2)	83 (7.6)	1 (0.1)
>38.9°C to 40.0°C	10 (0.9)	2 (0.2)	25 (2.3)	1 (0.1)
>40.0°C	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue[c]				
Any	677 (60.1)	457 (40.6)	726 (66.2)	264 (24.5)
Mild	278 (24.7)	250 (22.2)	232 (21.1)	133 (12.3)
Moderate	384 (34.1)	199 (17.7)	468 (42.7)	127 (11.8)
Severe	15 (1.3)	8 (0.7)	26 (2.4)	4 (0.4)
Headache[c]				
Any	623 (55.3)	396 (35.1)	708 (64.5)	264 (24.5)
Mild	361 (32.0)	256 (22.7)	302 (27.5)	170 (15.8)
Moderate	251 (22.3)	131 (11.6)	384 (35.0)	93 (8.6)
Severe	11 (1.0)	9 (0.8)	22 (2.0)	1 (0.1)
Chills[c]				
Any	311 (27.6)	109 (9.7)	455 (41.5)	74 (6.9)
Mild	195 (17.3)	82 (7.3)	221 (20.1)	53 (4.9)
Moderate	111 (9.8)	25 (2.2)	214 (19.5)	21 (1.9)
Severe	5 (0.4)	2 (0.2)	20 (1.8)	0 (0.0)
Vomiting[d]				
Any	31 (2.8)	10 (0.9)	29 (2.6)	12 (1.1)
Mild	30 (2.7)	8 (0.7)	25 (2.3)	11 (1.0)
Moderate	0 (0.0)	2 (0.2)	4 (0.4)	1 (0.1)
Severe	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

	COMIRNATY Dose 1 N[a]=1127 n[b] (%)	Placebo Dose 1 N[a]=1127 n[b] (%)	COMIRNATY Dose 2 N[a]=1097 n[b] (%)	Placebo Dose 2 N[a]=1078 n[b] (%)
Diarrhea[e]				
Any	90 (8.0)	82 (7.3)	65 (5.9)	44 (4.1)
Mild	77 (6.8)	72 (6.4)	59 (5.4)	39 (3.6)
Moderate	13 (1.2)	10 (0.9)	6 (0.5)	5 (0.5)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
New or worsened muscle pain[c]				
Any	272 (24.1)	148 (13.1)	355 (32.4)	90 (8.3)
Mild	125 (11.1)	88 (7.8)	152 (13.9)	51 (4.7)
Moderate	145 (12.9)	60 (5.3)	197 (18.0)	37 (3.4)
Severe	2 (0.2)	0 (0.0)	6 (0.5)	2 (0.2)
New or worsened joint pain[c]				
Any	109 (9.7)	77 (6.8)	173 (15.8)	51 (4.7)
Mild	66 (5.9)	50 (4.4)	91 (8.3)	30 (2.8)
Moderate	42 (3.7)	27 (2.4)	78 (7.1)	21 (1.9)
Severe	1 (0.1)	0 (0.0)	4 (0.4)	0 (0.0)
Use of antipyretic or pain medication[f]	413 (36.6)	111 (9.8)	557 (50.8)	95 (8.8)

Note: Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

a. N = Number of participants reporting at least 1 yes or no response for the specified event after the specified dose.

b. n = Number of participants with the specified reaction.

c. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.

d. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.

e. Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.

f. Severity was not collected for use of antipyretic or pain medication.

Unsolicited Adverse Events

In Study 2, 2,260 adolescents (1,131 COMIRNATY; 1,129 placebo) were 12 through 15 years of age. Of these, 634 (56.1%) participants in the COMIRNATY group and 629 (55.7%) participants in the placebo group had follow-up time between ≥4 months to <6 months after Dose 2 in the blinded placebo-controlled follow-up period with an additional 152 (13.4%) and 144 (12.8%) with ≥6 months of blinded follow-up time in the COMIRNATY and placebo groups, respectively.

A total of 1,113 (98.4%) participants 12 through 15 years of age originally randomized to COMIRNATY had ≥6 months total (blinded and unblinded) follow-up after Dose 2.

An analysis of all unsolicited adverse events in Study 2 from Dose 1 up to the participant unblinding date was conducted. Among participants 12 through 15 years of age who received at least one dose of study vaccine, unsolicited adverse events were reported by 95 (8.4%) participants in the COMIRNATY group and 113 (10.0%) participants in the placebo group.

In an analysis of all unsolicited adverse events reported during blinded follow-up from Dose 1 through 1 month after Dose 2, in adolescents 12 to 15 years of age, those assessed as adverse reactions not already captured by solicited local and systemic reactions were lymphadenopathy (9 vs. 2), and nausea (5 vs. 2).

In the analysis of blinded, placebo-controlled follow-up, there were no other notable patterns or numerical imbalances between treatment groups for specific categories of unsolicited adverse events (including other neurologic or neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to COMIRNATY. In the analysis of unblinded follow-up, there were no notable patterns of specific categories of non-serious adverse events that would suggest a causal relationship to COMIRNATY.

Serious Adverse Events
In Study 2, among participants 12 through 15 years of age who had received at least 1 dose of vaccine or placebo (COMIRNATY = 1,131; placebo = 1,129), serious adverse events from Dose 1 up to the participant unblinding date in ongoing follow-up were reported by 10 (0.9%) COMIRNATY recipients and 2 (0.2%) placebo recipients. In these analyses, 69.0% of study participants had at least 4 months of follow-up after Dose 2. In the analysis of blinded, placebo-controlled follow-up, there were no notable patterns between treatment groups for specific categories of serious adverse events (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to COMIRNATY. In the analysis of unblinded follow-up, there were no notable patterns of specific categories of serious adverse events that would suggest a causal relationship to COMIRNATY.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of COMIRNATY, including under Emergency Use Authorization. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Cardiac Disorders: myocarditis, pericarditis
Gastrointestinal Disorders: diarrhea, vomiting
Immune System Disorders: severe allergic reactions, including anaphylaxis, and other hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema)
Musculoskeletal and Connective Tissue Disorders: pain in extremity (arm)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to COMIRNATY during pregnancy. Women who are vaccinated with COMIRNATY during pregnancy are encouraged to enroll in the registry by visiting https://mothertobaby.org/ongoing-study/covid19-vaccines/.

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available data on COMIRNATY administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

A developmental toxicity study has been performed in female rats administered the equivalent of a single human dose of COMIRNATY on 4 occasions, twice prior to mating and twice during gestation. These studies revealed no evidence of harm to the fetus due to the vaccine *(see Animal Data)*.

Data

Animal Data

In a developmental toxicity study, 0.06 mL of a vaccine formulation containing the same quantity of nucleoside-modified messenger ribonucleic acid (mRNA) (30 mcg) and other ingredients included in a single human dose of COMIRNATY was administered to female rats by the intramuscular route on 4 occasions: 21 and 14 days prior to mating, and on gestation days 9 and 20. No vaccine-related adverse effects on female fertility, fetal development, or postnatal development were reported in the study.

8.2 Lactation

Risk Summary

It is not known whether COMIRNATY is excreted in human milk. Data are not available to assess the effects of COMIRNATY on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for COMIRNATY and any potential adverse effects on the breastfed child from COMIRNATY or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

Safety and effectiveness of COMIRNATY in individuals 12 through 17 years of age is based on safety and effectiveness data in this age group and in adults *[see Adverse Reactions (6) and Clinical Studies (14.1)]*.

The safety and effectiveness of COMIRNATY in individuals younger than 12 years of age have not been established.

8.5 Geriatric Use

Of the total number of COMIRNATY recipients in Study 2 as of March 13, 2021 (N = 22,026), 20.7% (n = 4,552) were 65 years of age and older and 4.2% (n = 925) were 75 years of age and older *[see Clinical Studies (14.1)]*. No overall differences in safety or effectiveness were observed between these recipients and younger recipients.

11 DESCRIPTION

COMIRNATY (COVID-19 Vaccine, mRNA) is a sterile suspension for injection for intramuscular use. COMIRNATY is supplied as a frozen suspension in multiple dose vials with purple caps and labels with purple borders; each vial must be diluted with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine. Each 0.3 mL dose of COMIRNATY supplied in multiple dose vials with purple caps and labels with purple borders contains 30 mcg of a nucleoside-modified messenger RNA (mRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2.

Each 0.3 mL dose of the COMIRNATY supplied in multiple dose vials with purple caps and labels with purple borders also includes the following ingredients:
lipids (0.43 mg ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate),
0.05 mg 2-(polyethylene glycol 2000)-N,N-ditetradecylacetamide,
0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potassium chloride,
0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate

dihydrate, and 6 mg sucrose. The diluent (sterile 0.9% Sodium Chloride Injection, USP) contributes an additional 2.16 mg sodium chloride per dose.

COMIRNATY does not contain preservative.

The vial stoppers are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The nucleoside-modified mRNA in COMIRNATY is formulated in lipid particles, which enable delivery of the mRNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits an immune response to the S antigen, which protects against COVID-19.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

COMIRNATY has not been evaluated for the potential to cause carcinogenicity, genotoxicity, or impairment of male fertility. In a developmental toxicity study in rats with COMIRNATY there were no vaccine-related effects on female fertility *[see Use in Specific Populations (8.1)]*.

14 CLINICAL STUDIES

14.1 Efficacy in Participants 16 Years of Age and Older

Study 2 is an ongoing, multicenter, multinational, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in participants 12 years of age and older. Randomization was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥56-year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, were included as were participants with known stable infection with HIV, hepatitis C virus (HCV), or hepatitis B virus (HBV).

In Study 2, based on data accrued through March 13, 2021, approximately 44,000 participants 12 years of age and older were randomized equally and received 2 doses of COMIRNATY or placebo. Participants are planned to be followed for up to 24 months, for assessments of safety and efficacy against COVID-19.

Overall, among the total participants who received COMIRNATY or placebo, 51.4% or 50.3% were male and 48.6% or 49.7% were female, 79.1% or 79.2% were 16 through 64 years of age, 20.9% or 20.8% were 65 years of age and older, 81.9% or 82.1% were White, 9.5% or 9.6% were Black or African American, 1.0% or 0.9% were American Indian or Alaska Native, 4.4% or 4.3% were Asian, 0.3% or 0.2% Native Hawaiian or other Pacific Islander, 25.6% or 25.4% were Hispanic/Latino, 73.9% or 74.1% were non-Hispanic/Latino, 0.5% or 0.5% did not report ethnicity, 46.0% or 45.7% had comorbidities [participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as subjects who had at least 1 of the Charlson comorbidity index category or body mass index (BMI) ≥30 kg/m^2], respectively. The mean age at vaccination was 49.8 or 49.7 years and median age was 51.0 or 51.0 in participants who received COMIRNATY or placebo, respectively.

Efficacy Against COVID-19

The population for the analysis of the protocol pre-specified primary efficacy endpoint included 36,621 participants 12 years of age and older (18,242 in the COMIRNATY group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. The population in the protocol pre-specified primary efficacy analysis included all participants 12 years of age and older who had been enrolled from July 27, 2020, and followed for the development of COVID-19 through November 14, 2020. Participants 18 through 55 years of age and 56 years of age and older began enrollment from July 27, 2020, 16 through 17 years of age began enrollment from September 16, 2020, and 12 through 15 years of age began enrollment from October 15, 2020.

For participants without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, vaccine efficacy against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0% (95% credible interval: 90.3, 97.6), which met the pre-specified success criterion. The case split was 8 COVID-19 cases in the COMIRNATY group compared to 162 COVID-19 cases in the placebo group.

The population for the updated vaccine efficacy analysis included participants 16 years of age and older who had been enrolled from July 27, 2020, and followed for the development of COVID-19 during blinded placebo-controlled follow-up through March 13, 2021, representing up to 6 months of follow-up after Dose 2. There were 12,796 (60.8%) participants in the COMIRNATY group and 12,449 (58.7%) in the placebo group followed for ≥4 months after Dose 2 in the blinded placebo-controlled follow-up period.

SARS-CoV-2 variants of concern identified from COVID-19 cases for this age group from this data cutoff include B.1.1.7 (Alpha) and B.1.351 (Beta). Representation of identified variants among cases in vaccine versus placebo recipients did not suggest decreased vaccine effectiveness against these variants.

The updated vaccine efficacy information is presented in Table 7.

Table 7: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Age Subgroup – Participants 16 Years of Age and Older Without Evidence of Infection and Participants With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	**COMIRNATY N[a]=19,993 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=20,118 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
All participants	77 6.092 (19,711)	833 5.857 (19,741)	91.1 (88.8, 93.1)
16 through 64 years	70 4.859 (15,519)	709 4.654 (15,515)	90.5 (87.9, 92.7)
65 years and older	7 1.233 (4192)	124 1.202 (4226)	94.5 (88.3, 97.8)

First COVID-19 occurrence from 7 days after Dose 2 in participants with or without* evidence of prior SARS-CoV-2 infection			
Subgroup	**COMIRNATY N[a]=21,047 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=21,210 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
All participants	81 6.340 (20,533)	854 6.110 (20,595)	90.9 (88.5, 92.8)
16 through 64 years	74 5.073 (16,218)	726 4.879 (16,269)	90.2 (87.5, 92.4)
65 years and older	7 1.267 (4315)	128 1.232 (4326)	94.7 (88.7, 97.9)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Subgroup analyses of vaccine efficacy (although limited by small numbers of cases in some subgroups) did not suggest meaningful differences in efficacy across genders, ethnic groups, geographies, or for participants with obesity or medical comorbidities associated with high risk of severe COVID-19.

Efficacy Against Severe COVID-19

Efficacy analyses of secondary efficacy endpoints supported benefit of COMIRNATY in preventing severe COVID-19. Vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 8) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COMIRNATY and placebo groups.

Table 8: Vaccine Efficacy – First Severe COVID-19 Occurrence in Participants 16 Years of Age and Older With or Without* Prior SARS-CoV-2 Infection Based on Protocol† or Centers for Disease Control and Prevention (CDC)‡ Definition From 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up

Vaccine Efficacy – First Severe COVID-19 Occurrence			
	COMIRNATY Cases n1[a] Surveillance Time[b] (n2[c])	**Placebo Cases n1[a] Surveillance Time[b] (n2[c])**	**Vaccine Efficacy % (95% CI[d])**
7 days after Dose 2[d]	1 6.353 (20,540)	21 6.237 (20,629)	95.3 (70.9, 99.9)
Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC Definition			
	COMIRNATY Cases n1[a] Surveillance Time[b] (n2[c])	**Placebo Cases n1[a] Surveillance Time[b] (n2[c])**	**Vaccine Efficacy % (95% CI[d])**
7 days after Dose 2[d]	0 6.345 (20,513)	31 6.225 (20,593)	100 (87.6, 100.0)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

† Severe illness from COVID-19 is defined in the protocol as confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, saturation of oxygen ≤93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen <300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

‡ Severe illness from COVID-19 as defined by CDC is confirmed COVID-19 and presence of at least 1 of the following:

- Hospitalization;
- Admission to the Intensive Care Unit;
- Intubation or mechanical ventilation;
- Death.

a. n1 = Number of participants meeting the endpoint definition.
b. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
c. n2 = Number of participants at risk for the endpoint.
d. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

14.2 Efficacy in Adolescents 12 Through 15 Years of Age

A descriptive efficacy analysis of Study 2 has been performed in 2,260 adolescents 12 through 15 years of age evaluating confirmed COVID-19 cases accrued up to a data cutoff date of September 2, 2021.

The vaccine efficacy information in adolescents 12 through 15 years of age is presented in Table 9.

Table 9: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2: Without Evidence of Infection and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period, Adolescents 12 Through 15 Years of Age Evaluable Efficacy (7 Days) Population

First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 through 15 years of age without evidence of prior SARS-CoV-2 infection*			
	COMIRNATY N[a]=1057 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=1030 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
Adolescents 12 through 15 years of age	0 0.343 (1043)	28 0.322 (1019)	100.0 (86.8, 100.0)
First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 through 15 years of age with or without evidence of prior SARS-CoV-2 infection			
	COMIRNATY N[a]=1119 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=1109 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
Adolescents 12 through 15 years of age	0 0.362 (1098)	30[f] 0.345 (1088)	100.0 (87.5, 100.0)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

d. n2 = Number of participants at risk for the endpoint.

e. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

f. The only SARS-CoV-2 variant of concern identified from COVID-19 cases in this age group from this data cutoff was B.1.1.7 (Alpha).

14.3 Immunogenicity in Adolescents 12 Through 15 Years of Age

In Study 2, an analysis of SARS-CoV-2 50% neutralizing titers (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated non-inferior immune responses (within 1.5-fold) comparing adolescents 12 through 15 years of age to participants 16 through 25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2 (Table 10).

Table 10: Summary of Geometric Mean Ratio for 50% Neutralizing Titer – Comparison of Adolescents 12 Through 15 Years of Age to Participants 16 Through 25 Years of Age (Immunogenicity Subset) – Participants Without Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population

		COMIRNATY		12 Through 15 Years/ 16 Through 25 Years	
		12 Through 15 Years n[a]=190	16 Through 25 Years n[a]=170		
Assay	Time Point[b]	GMT[c] (95% CI[c])	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])	Met Noninferiority Objective[e] (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer)[f]	1 month after Dose 2	1253.6 (1117.7, 1406.1)	708.1 (625.9, 801.1)	1.77 (1.50, 2.09)	Y

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic-acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence (up to 1 month after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 were included in the analysis.

a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. Protocol-specified timing for blood sample collection.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (Group 1 [12 through 15 years of age] – Group 2 [16 through 25 years of age]) and the corresponding CI (based on the Student t distribution).
e. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
f. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

16 HOW SUPPLIED/STORAGE AND HANDLING

COMIRNATY Suspension for Intramuscular Injection, multiple dose vials with purple caps and labels with purple borders are supplied in a carton containing 25 multiple dose vials (NDC 0069-1000-03) or 195 multiple dose vials (NDC 0069-1000-02). A 0.9% Sodium Chloride Injection, USP diluent is provided but shipped separately, and should be stored at controlled room temperature 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. The provided 0.9% Sodium Chloride Injection, USP diluent will be supplied either as cartons of 10 mL single-use vials manufactured by Hospira, Inc (NDC 0409-4888-10), or 2 mL single-use vials manufactured by Fresenius Kabi USA, LLC (NDC 63323-186-02).

After dilution, 1 vial contains 6 doses of 0.3 mL.

During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

Do not refreeze thawed vials.

Frozen Vials Prior to Use

Cartons of COMIRNATY multiple dose vials with purple caps and labels with purple borders arrive in thermal containers with dry ice. Once received, remove the vial cartons immediately from the thermal container and

preferably store in an ultra-low temperature freezer between -90ºC to -60ºC (-130ºF to -76ºF) until the expiry date printed on the label.

Alternatively, vials may be stored at -25°C to -15°C (-13°F to 5°F) for up to 2 weeks. Vials must be kept frozen and protected from light, in the original cartons, until ready to use. Vials stored at -25°C to -15°C (-13°F to 5°F) for up to 2 weeks may be returned 1 time to the recommended storage condition of -90ºC to -60ºC (-130ºF to -76ºF). Total cumulative time the vials are stored at -25°C to -15°C (-13°F to 5°F) should be tracked and should not exceed 2 weeks.

If an ultra-low temperature freezer is not available, the thermal container in which COMIRNATY arrives may be used as temporary storage when consistently re-filled to the top of the container with dry ice. Refer to the re-icing guidelines packed in the original thermal container for instructions regarding the use of the thermal container for temporary storage. The thermal container maintains a temperature range of -90ºC to -60ºC (-130ºF to -76ºF). Storage of the vials between -96°C to -60°C (-141°F to -76°F) is not considered an excursion from the recommended storage condition.

Transportation of Frozen Vials

If local redistribution is needed and full cartons containing vials cannot be transported at -90°C to -60°C (-130°F to -76°F), vials may be transported at -25°C to -15°C (-13°F to 5°F). Any hours used for transport at -25°C to -15°C (-13°F to 5°F) count against the 2-week limit for storage at -25°C to -15°C (-13°F to 5°F). Frozen vials transported at -25°C to -15°C (-13°F to 5°F) may be returned 1 time to the recommended storage condition of -90ºC to -60ºC (-130ºF to -76ºF).

Thawed Vials Before Dilution

Thawed Under Refrigeration

Thaw and then store undiluted vials in the refrigerator [2ºC to 8ºC (35ºF to 46ºF)] for up to 1 month. A carton of 25 vials or 195 vials may take up to 2 or 3 hours, respectively, to thaw in the refrigerator, whereas a fewer number of vials will thaw in less time.

Thawed at Room Temperature

For immediate use, thaw undiluted vials at room temperature [up to 25ºC (77ºF)] for 30 minutes. Thawed vials can be handled in room light conditions.

Vials must reach room temperature before dilution.

Undiluted vials may be stored at room temperature for no more than 2 hours.

Transportation of Thawed Vials

Available data support transportation of 1 or more thawed vials at 2°C to 8°C (35°F to 46°F) for up to 12 hours.

Vials After Dilution

After dilution, store vials between 2°C to 25°C (35°F to 77°F) and use within 6 hours from the time of dilution. During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light. Any vaccine remaining in vials must be discarded after 6 hours. Do not refreeze.

17 PATIENT COUNSELING INFORMATION

Inform vaccine recipient of the potential benefits and risks of vaccination with COMIRNATY.

Inform vaccine recipient of the importance of completing the 2 dose vaccination series.

There is a pregnancy exposure registry for COMIRNATY. Encourage individuals exposed to COMIRNATY around the time of conception or during pregnancy to register by visiting https://mothertobaby.org/ongoing-study/covid19-vaccines/.

Advise vaccine recipient to report any adverse events to their healthcare provider or to the Vaccine Adverse Event Reporting System at 1-800-822-7967 and www.vaers.hhs.gov.

Prior to administering the vaccine, give the vaccine recipient the Vaccine Information Fact Sheet for Recipients and Caregivers about COMIRNATY (COVID-19 Vaccine, mRNA) and the Pfizer-BioNTech COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19) for Use in Individuals 12 Years of Age and Older. The Vaccine Information Fact Sheet for Recipients and Caregivers is available at www.cvdvaccine-us.com.

This product's labeling may have been updated. For the most recent prescribing information, please visit https://dailymed.nlm.nih.gov/dailymed/.

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EXHIBIT 8

Article

BNT162b vaccines protect rhesus macaques from SARS-CoV-2

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A safe and effective vaccine against COVID-19 is urgently needed in quantities that are sufficient to immunize large populations. Here we report the preclinical development of two vaccine candidates (BNT162b1 and BNT162b2) that contain nucleoside-modified messenger RNA that encodes immunogens derived from the spike glycoprotein (S) of SARS-CoV-2, formulated in lipid nanoparticles. BNT162b1 encodes a soluble, secreted trimerized receptor-binding domain (known as the RBD–foldon). BNT162b2 encodes the full-length transmembrane S glycoprotein, locked in its prefusion conformation by the substitution of two residues with proline (S(K986P/V987P); hereafter, S(P2) (also known as P2 S)). The flexibly tethered RBDs of the RBD–foldon bind to human ACE2 with high avidity. Approximately 20% of the S(P2) trimers are in the two-RBD 'down', one-RBD 'up' state. In mice, one intramuscular dose of either candidate vaccine elicits a dose-dependent antibody response with high virus-entry inhibition titres and strong T-helper-1 $CD4^+$ and $IFN\gamma^+CD8^+$ T cell responses. Prime–boost vaccination of rhesus macaques (*Macaca mulatta*) with the BNT162b candidates elicits SARS-CoV-2-neutralizing geometric mean titres that are 8.2–18.2× that of a panel of SARS-CoV-2-convalescent human sera. The vaccine candidates protect macaques against challenge with SARS-CoV-2; in particular, BNT162b2 protects the lower respiratory tract against the presence of viral RNA and shows no evidence of disease enhancement. Both candidates are being evaluated in phase I trials in Germany and the USA[1–3], and BNT162b2 is being evaluated in an ongoing global phase II/III trial (NCT04380701 and NCT04368728).

Owing to the effects of the current pandemic of coronavirus disease 2019 (COVID-19) on human health and society, several collaborative research programmes have been launched and have generated insights and progress in vaccine development. Soon after emerging in December 2019, SARS-CoV-2 was identified as a betacoronavirus with high sequence similarity to bat-derived SARS-like coronaviruses[4,5]. The fast availability of vaccines is critical in the pandemic, and the rapid globalized response is mirrored by the upload of over 212,000 viral genome sequences as of 23 November 2020 to the Global Initiative on Sharing All Influenza Data.

The trimeric S of SARS-CoV-2 is a key target for virus-neutralizing antibodies[6] and the prime candidate for vaccine development. S binds its cellular receptor ACE2 through an RBD, which is part of S1 (the N-terminal furin cleavage fragment of S)[7,8]. On S, the RBDs are in 'up' positions, in which the receptor-binding sites and their dense cluster of neutralizing epitopes are exposed, or in 'down' positions, in which

A list of affiliations appears at the end of the paper.

the receptor-binding sites are buried but some S neutralizing epitopes on and off the RBDs remain available[9–12]. S rearranges to translocate the virus into cells by membrane fusion[9,13]. The C-terminal furin cleavage fragment of S (S2) contains the fusion machinery[14].

Messenger RNA (mRNA) technology allows the versatile design of vaccine antigens as well as highly scalable and fast manufacturing. With efficient lipid-nanoparticle-formulation processes, RNA vaccines are highly suited to the rapid development and supply needed during a pandemic[15]. RNA generated from DNA templates by a highly productive, cell-free in vitro transcription process is molecularly well-defined and free of materials of animal origin. Here we report the preclinical development of lipid-nanoparticle-formulated, N^1-methyl-pseudouridine (m1Ψ) nucleoside-modified mRNA (modRNA) BNT162b vaccine candidates (BNT162b1 and BNT162b2) that encode immunogens derived from the S of SARS-CoV-2 (Fig. 1a). The m1Ψ modification dampens innate immune sensing and—together with optimized noncoding sequence elements—increases the efficiency of RNA translation in vivo[16–18]. Vaccines based on modRNA have proven to be immunogenic for several viral targets[19,20].

Both of the BNT162b vaccines are being evaluated in phase I clinical trials in the USA (NCT04368728) and Germany (NCT04380701, EudraCT: 2020-001038-36), and BNT162b2 is being evaluated in a global phase II/III safety and efficacy study[1–3].

Construct design and analysis of expressed antigen

BNT162b1 RNA encodes the RBD with the SARS-CoV-2 S signal peptide fused to its N terminus (to enable endoplasmic reticulum translocation and secretion) and with the trimerization domain (foldon) of T4 fibritin[21] fused to its C terminus for multimeric display. BNT162b2 RNA encodes full-length S that is stabilized in the prefusion conformation by substitution of residues 986 and 987 to proline (that is, S(P2))[10,22,23] (Fig. 1a). The microfluidic capillary electrophoresis profiles of both of the RNAs show single sharp peaks that are consistent with their calculated lengths, indicating high purity and integrity (Fig. 1b). We detected robust expression of RBD–foldon or S(P2) by flow cytometry upon transfection of HEK293T cells with BNT162b1 RNA or BNT162b2 RNA formulated as lipid nanoparticles or mixed with a transfection reagent, respectively (Extended Data Fig. 1a). In transfected cells, the BNT162b1-encoded RBD or BNT162b2-encoded S(P2) localized to the secretory pathway, as shown by immunofluorescence microscopy (Extended Data Fig. 1b). We performed western blot under denaturing and non-denaturing conditions, and detected a main band of RBD-containing protein with an apparent molecular mass of more than 75 kDa (together with lesser quantities of a faster-migrating species) in the medium of cells transfected with BNT162b1 RNA, consistent with the secretion of trimeric RBD–foldon (which has a predicted molecular mass of 88.4 kDa) (Extended Data Fig. 1c).

For further structural characterization, we expressed the RBD–foldon and S(P2) antigens from DNA that corresponds to the RNA coding sequences. We purified the RBD–foldon from the medium of transfected Expi293F cells by affinity capture with the peptidase domain of ACE2 immobilized on agarose beads, which left little residual RBD–foldon uncaptured from the medium. We obtained evidence that the RBD–foldon has three RBDs flexibly tethered to a central hub using electron microscopy, which revealed a variety of conformations (Fig. 1c). The trimerized RBD bound to the peptidase domain of human ACE2 with an apparent K_D of less than 5 pM, which is 1,000-fold the reported K_D (5 nM) for monomeric RBD and is consistent with the avidity effect of multivalent binding that is enabled by the flexible tethering (Extended Data Fig. 1d). Although the flexibility of the RBD–foldon precluded direct structural analysis at high resolution, one RBD per trimer could be immobilized by binding to a complex of ACE2 and the B^0AT1 neutral amino acid transporter (which is chaperoned by ACE2) when that complex was in the previously reported closed conformation[8]

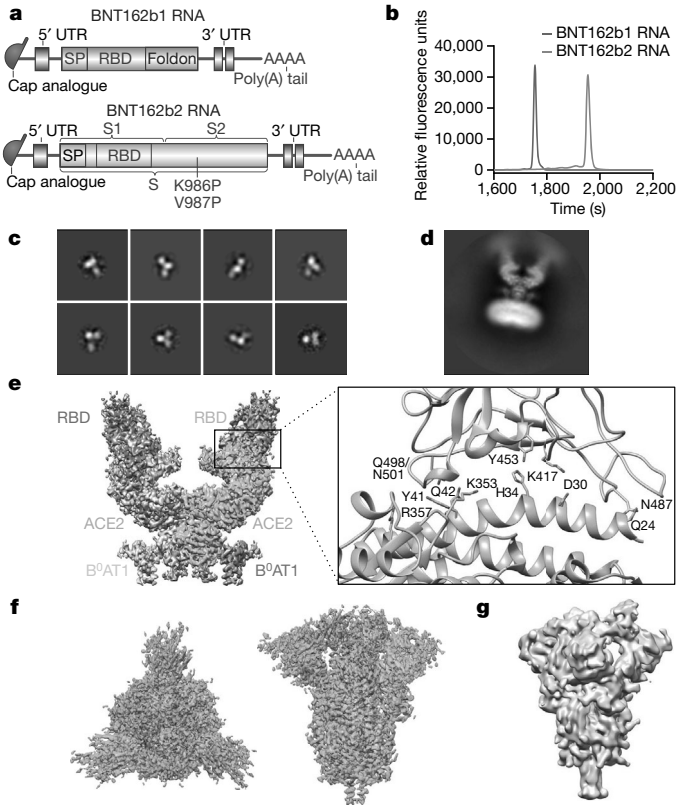

Fig. 1 | Vaccine design and characterization of the expressed antigens. **a**, Structure of BNT162b1 and BNT162b2 RNA. UTR, untranslated region; SP, signal peptide. The proline subsitutions of S(P2) (K986P and V897P) are indicated. **b**, Liquid capillary electropherograms of in vitro-transcribed BNT162b1 and BNT162b2 RNA. Peaks represent individual samples merged into one graph. **c**, Representative 2D class averages from electron microscopy of negatively stained RBD–foldon trimers. Box edge, 37 nm. **d**, Two-dimensional class average from cryo-EM of the ACE2–B^0AT1–RBD–foldon trimer complex. Long box edge, 39.2 nm. Peripheral to the relatively well-defined density of each RBD domain bound to ACE2, there is diffuse density that we attribute to the remainder of the flexibly tethered RBD–foldon trimer. A detergent micelle forms the density at the end of the complex opposite the RBD–foldon. **e**, Density map of the ACE2–B^0AT1–RBD–foldon trimer complex at 3.24 Å, after focused refinement of the ACE2 extracellular domain bound to a RBD monomer. Surface colour-coding is by subunit. The ribbon model refined to the density shows the RBD–ACE2 binding interface.Residues that potentially mediate polar interactions are labelled. **f**, A 3.29 Å cryo-EM map of S(P2) with fitted and refined atomic model, viewed down the threefold axis towards the membrane (left) and viewed perpendicular to the threefold axis (right). The map is coloured by protomer. **g**, Mass density map of TwinStrep-tagged S(P2) produced by 3D classification of images extracted from cryo-EM micrographs with no symmetry averaging, showing the class in the one-RBD-up and two-RBD-down position.

(Fig. 1d). The size and symmetry of the RBD–foldon–ACE2–B^0AT1 ternary complex aided image reconstruction by cryo-electron microscopy (cryo-EM), and we determined the structure of the RBD in the complex to a resolution of 3.24 Å (Fig. 1e, Extended Data Table 1, Supplementary Fig. 2). One copy of the RBD was resolved for each bound trimer. The binding interface between the resolved RBD and the extracellular domain of ACE2 was fitted to a previously reported structure[7], and showed good agreement. The high-avidity binding to ACE2 and well-resolved structure in complex with ACE2 demonstrate that the recombinant RBD–foldon authentically presents the ACE2-binding site that is targeted by many SARS-CoV-2-neutralizing antibodies[11,24].

We affinity-purified the trimeric S(P2) from detergent-solubilized protein via a C-terminal TwinStrep tag. S(P2) bound the peptidase

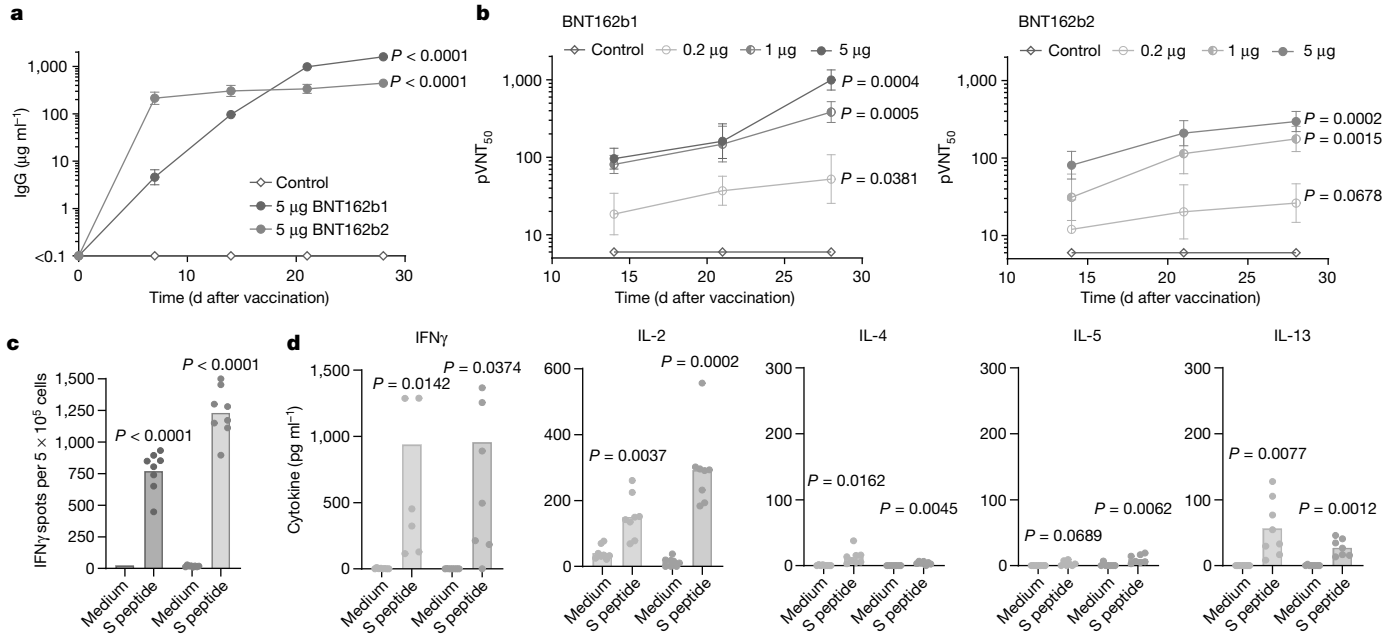

Fig. 2 | Mouse immunogenicity. We injected BALB/c mice ($n = 8$) intramuscularly with a single dose of one of the BNT162b vaccine candidates or a buffer control. Geometric means of each group ± 95% confidence interval are shown. Day-28 *P* values compared to control (multiple comparison of mixed-effect analysis using Dunnett's multiple comparisons test) for the single time points and groups are provided in **a**, **b**. **a**, Levels of RBD-specific IgG in sera of mice immunized using 5 μg of BNT162b1 or BNT162b2, determined by enzyme-linked immunosorbent assay (ELISA). For day-0 values, a prescreening of randomly selected mice was performed ($n = 4$). Extended Data Figure 3a, b shows IgG levels with lower BNT162b doses and sera testing for detection of S1. **b**, Pseudovirus-based VSV-SARS-CoV-2 50% neutralization titres ($pVNT_{50}$) in sera of mice immunized using BNT162b1 (left) or BNT162b2 (right). Extended Data Figure 3g–i provides the number of infected cells per well with serum samples drawn 28 d after injection and titre correlation to a SARS-CoV-2 virus neutralization assay. For cellular response analysis in **c**, **d**, splenocytes of BALB/c mice ($n = 8$, unless stated otherwise) injected intramuscularly with BNT162b1 (green) or BNT162b2 (pink) were restimulated ex vivo with full-length S peptide mix or cell culture medium. Symbols represent individual mice. Heights of bars indicate the mean. *P* values compare immunized groups with the control (parametric, two-tailed paired *t*-test). **c**, IFNγ ELISpot of splenocytes 12 d after injection with 5 μg of one of the BNT162b vaccines. **d**, Cytokine production by splenocytes 28 d after injection with 0.2 μg BNT162b1 or 1 μg BNT162b2, determined by bead-based multiplex analysis (BNT162b2: $n = 7$ for IL-4, IL-5 and IL-13, one outlier removed by the ROUT method ($Q = 1\%$) for the S peptide stimulated samples).

domain of human ACE2 and a human anti-RBD neutralizing antibody (B38) with high affinity[25] (an apparent K_D of 1 nM for each) (Extended Data Fig. 1e, f). Our structural analysis by cryo-EM produced a mass density map at a nominal resolution of 3.29 Å, into which we fitted and rebuilt a previously published atomic model[10] (Fig. 1f, Extended Data Fig. 2a, b, Extended Data Table 1). The rebuilt model showed good agreement with previously reported structures of prefusion full-length wild-type S and its ectodomain with the P2 mutations[9,10]. Three-dimensional classification of the dataset showed a class of particles that was in a one-RBD up (accessible for receptor binding), two-RBD down (closed) conformation; this class represented 20.4% of the trimeric molecules (Fig. 1g, Extended Data Fig. 2c). The remainder of the trimeric molecules were in an all-RBD down conformation. The RBD in the up conformation was less well-resolved than the other parts of the structure, which suggests conformational flexibility and a dynamic equilibrium between the RBD up and RBD down states, as has previously been suggested[9,26]. Our binding and structural analyses indicate that the BNT162b2 RNA sequence encodes a recombinant S(P2) that can authentically present the ACE2-binding site and other epitopes that are targeted by SARS-CoV-2-neutralizing antibodies.

BNT162b-elicted immunogenicity in mice

To study vaccine immunogenicity, we characterized B and T cell responses in a series of experiments in BALB/c mice after a single intramuscular injection of 0.2, 1 or 5 μg of BNT162b1 or BNT162b2, or of a buffer control. A single immunization using either of the candidate vaccines induced high titres of RBD- and S1-binding serum IgG in a dose-level-dependent manner (Fig. 2a, Extended Data Fig. 3a–d); these titres increased more steeply for BNT162b2. On day 28 after injection with 5 μg BNT162b1 or BNT162b2, geometric mean endpoint titres of RBD-binding serum IgG were 752,680 or 434,560, respectively. Polyclonal IgG elicited by either of the candidate vaccines had strong apparent binding affinity for a recombinant RBD target antigen (geometric mean apparent K_D of 717 pM for BNT162b1 and 993 pM for BNT162b2), with a low apparent off-rate and a high apparent on-rate (Extended Data Fig. 3e). Serum samples from buffer-immunized control mice had no detectable RBD- or S1-specific IgG (Fig. 2a, b, Extended Data Fig. 3a–d), and neither did serum samples from mice injected up to two times with equivalent modRNA, formulated in lipid nanoparticles, that encoded a SARS-CoV-2 irrelevant antigen (data not shown).

We measured the inhibition of virus entry by BNT162b-immunized mouse serum in a neutralization assay using vesicular stomatitis virus (VSV)-based SARS-CoV-2 pseudovirus. As with the antigen-specific IgG geometric mean titres (GMTs), 50% pseudovirus-neutralization GMTs increased steadily after injection of 5 μg of either candidate vaccine, and reached 1,056 for BNT162b1 and 296 for BNT162b2 on day 28 after injection (Fig. 2b, Extended Data Fig. 3f, g). We tested a random selection of samples in a SARS-CoV-2 neutralization assay, which demonstrated strong correlation of pseudovirus and SARS-CoV-2 neutralization (Pearson correlation of 0.9479 between the tests) (Extended Data Fig. 3h). In summary, each candidate vaccine induced a high functional antibody response in mice, and BNT162b1 induced higher titres than BNT162b2 after one injection.

Our characterization of antigen-specific responses of splenic T cells in mice at 12 and 28 days after injection with the BNT162b vaccines

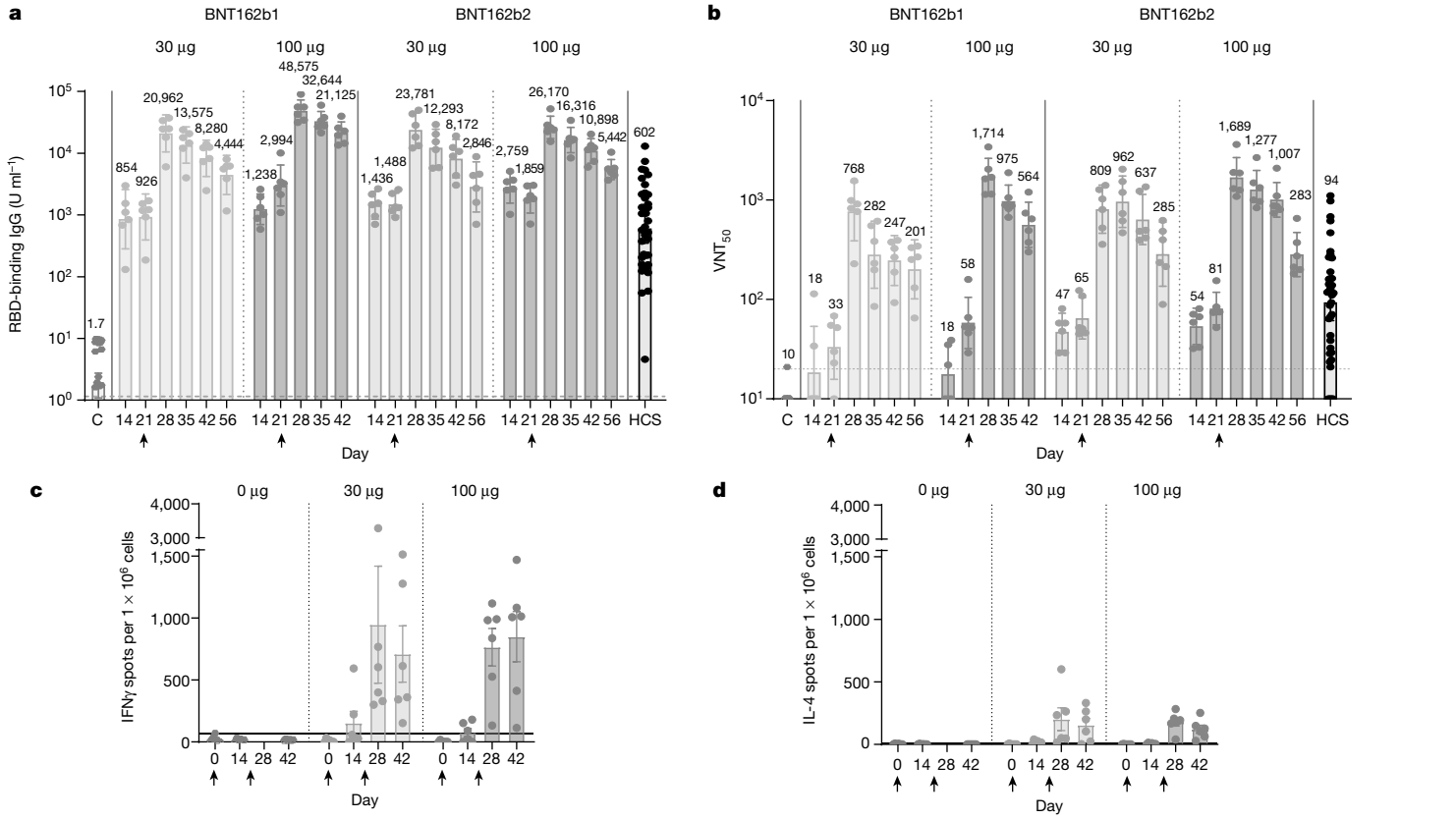

Fig. 3 | Macaque immunogenicity. Male macaques (2–4 years old) were injected on day 0 and day 21 (arrows below the *x*-axes indicate the day of second injection) with 30 µg or 100 µg of BNT162b1 (green) or BNT162b2 (pink) ($n = 6$ each). Additional macaques received saline (control (C), $n = 9$)). Human convalescent sera (HCS) were obtained from patients infected with SARS-CoV-2 at least 14 d after PCR-confirmed diagnosis and at a time when acute COVID-19 symptoms had resolved ($n = 38$). The HCS panel is a benchmark for serology studies in this Article and previous publications[1–3]. **a**, Concentrations (in arbitrary units) of IgG that binds recombinant SARS-CoV-2 RBD (lower limit of detection (LLOD) = 1.72 U ml^{-1}). **b**, SARS-CoV-2 50% virus-neutralization titres (VNT_{50}) (LLOD = 20). **c**, **d**, Peripheral blood mononuclear cells collected on days 0, 14, 28 and 42 after first injection of BNT162b2 were restimulated ex vivo with full-length S peptide mix. Arrows below the *x*-axis indicate the days of dose 1 and dose 2. **c**, IFNγ ELISpot. **d**, IL-4 ELISpot. Heights of bars indicate the geometric (**a**, **b**) or arithmetic (**c**, **d**) means for each group, and values are written above the bars (**a**, **b**). Whiskers indicate 95% confidence intervals (**a**, **b**) or s.e.m. (**c**, **d**). Each symbol represents one macaque. Horizontal dashed line marks the LLOD. Values below the LLOD were set to 1/2 the LLOD.

revealed a high fraction of $CD4^+$ and $CD8^+$ T cells that produced IFNγ and $CD8^+$ cells that produced IL-2, as shown by enzyme-linked immunospot assay (ELISpot) or intracellular-cytokine-staining flow cytometry analysis after ex vivo restimulation with a full-length S peptide pool (Fig. 2c, Extended Data Fig. 4a, b). Total splenocytes collected on day 28 and restimulated with the full-length S peptide pool secreted high levels of the T-helper-1 (T_H1) cytokines IL-2 or IFNγ, and minute or undetectable levels of the T-helper-2 (T_H2) cytokines IL-4, IL-5 or IL-13, as measured in multiplex immunoassays (Fig. 2d). Overall, the patterns of $CD4^+$ and $CD8^+$ T cell responses were similar for the two vaccine candidates, with a somewhat stronger IFNγ-producing $CD8^+$ T cell response in mice immunized with BNT162b2.

We assessed vaccine-induced effects on the proliferation and dynamics of immune-cell populations in injection-site draining lymph nodes (to evaluate the principal immune-educated compartments for proficient T and B cell priming) as well as in blood and spleen (to evaluate systemic effects of the vaccines). We observed higher numbers of plasma cells, class-switched $IgG1^+$ and $IgG2a^+$ B cells, and germinal-centre B cells in draining lymph nodes, and higher numbers of class-switched $IgG1^+$ and germinal-centre B cells in spleens of mice at 12 days after injection with 5 µg of either vaccine as compared to control (Extended Data Fig. 4c, d). Vaccine-immunized mice had significantly fewer circulating B cells than did control mice as measured in blood at day 7 after injection (Extended Data Fig. 4e), which may imply that B cell homing to lymphoid compartments contributed to augmented B cell counts in the draining lymph nodes and spleen.

The draining lymph nodes from BNT162b1- or BNT162b2-immunized mice also displayed significantly higher counts of $CD8^+$ and $CD4^+$ T cells (as compared to buffer-immunized mice) at 12 days after injection, which were most pronounced for T follicular helper (T_{FH}) cells—including the $ICOS^+$ subsets that are essential for the formation of germinal centres (Extended Data Fig. 4c). Both of the BNT162b vaccines increased T_{FH} cell counts in the spleen and blood, whereas an increase in circulating $CD8^+$ T cells was detected only in BNT162b2-immunized mice (Extended Data Fig. 4d, e). In aggregate, these data indicate a strong induction of SARS-CoV-2-pseudovirus neutralization titres and systemic $CD8^+$ and T_H1-driven $CD4^+$ T-cell responses by both of the vaccine candidates, and a somewhat more-pronounced cellular response to BNT162b2.

BNT162b-elicted immunogenicity in macaques

To assess the immunogenicity of BNT162b1 and BNT162b2 in nonhuman primates, we intramuscularly injected groups of six macaques (male, 2–4 years old) with 30 or 100 µg of BNT162b1, BNT162b2 or saline control on day 0 (dose 1) and day 21 (dose 2). RBD-binding IgG was readily detectable by day 14 after dose 1, and levels had increased further 7 days after dose 2 (day 28) (Fig. 3a). On day 28, geometric mean concentrations of RBD-binding IgG were 20,962 units (U) ml^{-1} (at 30-µg dose level) and 48,575 U ml^{-1} (at 100-µg dose level) for BNT162b1, and

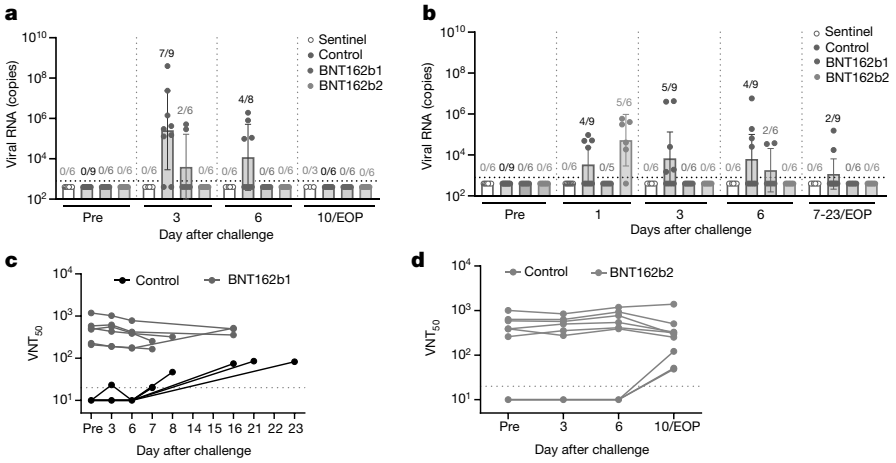

Fig. 4 | Virological and serological evidence of protection of macaques from challenge with infectious SARS-CoV-2. Macaques that had been immunized using 100 μg of BNT162b1 or BNT162b2 ($n = 6$ each) or mock-immunized with saline challenge (control) ($n = 9$) were challenged with 1.05×10^6 total plaque-forming units of SARS-CoV-2 split equally between the intranasal and intratracheal routes. Additional macaques (sentinel) ($n = 6$) were mock-challenged with cell culture medium. Macaque assignments to cohorts and schedules of immunization, challenge and sample collection are provided in Extended Data Fig. 6, Extended Data Table 2. Viral RNA levels were detected by RT–qPCR. **a**, Viral RNA in bronchoalveolar lavage fluid. 'Pre', before challenge; 10/EOP, day 10 or end of the project. **b**, Viral RNA in nasal swabs; 7–23/EOP, days 7–23 or end of project. Symbols represent individual macaques. Ratios above bars indicate the number of viral-RNA-positive macaques among all macaques in a group with evaluable samples. Heights of bars indicate geometric mean viral RNA copies; whiskers indicate geometric s.d. Dotted lines indicate LLOD. Values below the LLOD were set to 1/2 the LLOD. Two-sided statistical significance by a nonparametric test (Friedman's test) of differences in viral RNA detection after challenge between six BNT162b1-immunized and six mock-immunized macaques (challenge cohorts 1 and 2) was $P = 0.0152$ for bronchoalveolar lavage fluid and $P = 0.0048$ for nasal swab; between six BNT162b2-immunized macaques and three mock-immunized macaques (challenge cohort 3), the statistical significance was $P = 0.0014$ for bronchoalveolar lavage fluid and $P = 0.2622$ for nasal swabs. Serum samples were assayed for SARS-CoV-2 VNT_{50}. **c**, BNT162b1-immunized macaques and controls (challenge cohorts 1 and 2). **d**, BNT162b2-immunized macaques and controls (challenge cohort 3). Symbols represent titres from individual macaques. Horizontal dashed line indicates the lower limit of quantification of 20.

23,781 U ml^{-1} (30-μg dose level) and 26,170 U ml^{-1} (100-μg dose level) for BNT162b2. For comparison, the geometric mean concentration of RBD-binding IgG of a panel of 38 SARS-CoV-2-convalescent human sera was 602 U ml^{-1}, which is lower than the geometric mean concentration of the immunized macaques after one or two doses.

Fifty per cent virus-neutralization GMTs—measured by a SARS-CoV-2-neutralization assay[27] (rather than a pseudovirus-neutralization assay)—were detectable in the sera of most BNT162b1-immunized macaques by day 21 after dose 1, and in all BNT162b2-immunized macaques by day 14 after dose 1 (Fig. 3b). There was a strong boosting effect; comparable peak measured GMTs were elicited by BNT162b1 (768 for 30 μg and 1,714 for 100 μg) and BNT162b2 (962 for 30 μg and 1,689 for 100 μg), as measured in sera drawn 7 or 14 days after dose 2. For BNT162b2, sera were available up to day 56 after dose 1 (28 days after dose 2); robust GMTs of 285 for 30-μg and 283 for 100-μg dose levels persisted to this time point. For comparison, the neutralization GMT of the human convalescent sera was 94, which is substantially lower than the GMTs of macaque sera drawn 21 or 35 days after dose 2.

We analysed the S-specific T cell responses of BNT162b2- or saline-injected macaques using peripheral blood mononuclear cells collected before immunization and at the times indicated after doses 1 and 2. ELISpot demonstrated strong IFNγ, but minimal IL-4, responses after dose 2 (Fig. 3c, d, Extended Data Fig. 5a). Intracellular cytokine staining confirmed that BNT162b2 elicited a high frequency of $CD4^+$ T cells that produced IFNγ, IL-2 or TNF, but a low frequency of $CD4^+$ T cells that produced IL-4, which indicates a T_H1-biased response (Extended Data Fig. 5b, c). Intracellular cytokine staining also demonstrated that BNT162b2 elicited circulating S-specific $CD8^+$ T cells that produced IFNγ (Extended Data Fig. 5d).

BNT162b-elicted protection in macaques

Forty-one to fifty-five days after dose 2, six of the 2–4-year-old macaques that had been immunized using 100 μg BNT162b1, and six that had been immunized using 100 μg BNT162b2, were challenged with 1.05×10^6 plaque-forming units of SARS-CoV-2 (strain USA-WA1/2020) split equally between the intranasal and intratracheal routes, as previously described[28] (Extended Data Fig. 6, Extended Data Table 2). In addition, nine age-matched macaques (controls) that had been mock-immunized with saline received the same SARS-CoV-2 challenge, and six age-matched macaques (sentinels)—three of which had been immunized using 30 μg BNT162b2—were mock-challenged with cell culture medium. We collected nasal, oropharyngeal and rectal swabs, and performed bronchoalveolar lavage at the times indicated (Extended Data Table 2). We then tested samples for SARS-CoV-2 RNA (genomic RNA and subgenomic transcripts) using reverse-transcription quantitative polymerase chain reaction (RT–qPCR). All personnel who performed clinical, radiological, histopathological or RT–qPCR evaluations were blinded to the group assignments of the macaques.

Viral RNA was detected in bronchoalveolar lavage fluid from seven of nine control macaques on day 3; from four of eight control macaques on day 6 after challenge (with one indeterminant result); and from none of the six control macaques that underwent bronchoalveolar lavage at the end of project (EOP; days 7–23 after challenge) (Fig. 4a). Viral RNA was detected in the bronchoalveolar lavage fluid of two of six BNT162b1-immunized macaques on day 3 after challenge, and from none thereafter. Viral RNA was not detected in bronchoalveolar lavage fluid from the BNT162b2-immunized, SARS-CoV-2 challenged macaques at any of the time points we sampled.

In nasal swabs obtained on the day after challenge, viral RNA was detected from control-immunized macaques (4 of 9) and BNT162b2-immunized macaques (5 of 6), but not from BNT162b1-immunized macaques (Fig. 4b). In subsequent nasal swabs, viral RNA was detected from some of the control-immunized macaques at each sampling time point (5 of 9 on day 3, 4 of 9 on day 6 and 2 of 9 on days 7–23), from some BNT162b1-immunized macaques at only one sampling time point (2 of 6 on day 6) and from none of the BNT162b2-immunized macaques at any sampling time point. Similar patterns were seen in oropharyngeal and

rectal swabs: viral RNA was more often detected in control-immunized macaques than in BNT162b1- or BNT162b2-immunized macaques, and there was more persistence of viral RNA in rectal swabs than in oropharyngeal swabs (Extended Data Fig. 7a, b).

At the time of challenge, SARS-CoV-2-neutralizing titres ranged from 208 to 1,185 in the BNT162b1-immunized macaques and from 260 to 1,004 in the BNT162b2-immunized macaques. Neutralizing titres were below the limit of detection in the control macaques (Fig. 4c, d). The control macaques responded to challenge with infectious virus with an increase in SARS-CoV-2-neutralizing titres, consistent with an immune response to viral infection. However, there was no trend towards increasing SARS-CoV-2-neutralizing titres in response to viral challenge in the BNT162b1-immunized or BNT162b2-immunized macaques, consistent with their immunization suppressing SARS-CoV-2 infection. The maximum SARS-CoV-2-neutralizing titre elicited by virus challenge of control macaques remained below 150 through to the time of necropsy, whereas all immunized macaques maintained neutralizing titres greater than 150 throughout the challenge experiment.

None of the challenged macaques—whether immunized or not—showed clinical signs of illness (Extended Data Fig. 7c–f). Radiographic abnormalities were generally minimal or mild, and were not consistently associated with viral challenge (Extended Data Fig. 8a, b). The histopathology of necropsy specimens obtained 7–8 days after challenge revealed localized areas of pulmonary inflammation that were limited in extent even in the control macaques challenged after mock immunization with saline (Extended Data Fig. 8c). We conclude that the 2–4-year-old male-macaque challenge model is primarily a model of SARS-CoV-2 infection rather a model than of COVID-19 diseae.

Discussion

We demonstrate that the candidate vaccines BNT162b1 or BNT162b2—lipid-nanoparticle-formulated, m1Ψ nucleoside-modified mRNAs that encode secreted, trimerized SARS-CoV-2 RBD or prefusion-stabilized S, respectively—induce strong antigen-specific immune responses in mice and macaques. The RBD–foldon coding sequence directs the expression and secretion of a flexible, trimeric protein that binds to ACE2 with high affinity and has structurally intact ACE2 receptor-binding sites. We confirmed that protein expressed from DNA with the BNT162b2-encoded S(P2) amino acid sequence was in the prefusion conformation using cryo-EM. This analysis showed that the antigenically important RBD can assume the up conformation, in which the receptor-binding site that is rich in neutralizing epitopes is accessible in a proportion of the molecules[24]. The alternative states observed probably reflect a dynamic equilibrium between RBD up and down positions[10,26]. The binding of expressed and purified S(P2) to ACE2 and a neutralizing monoclonal antibody further demonstrates the conformational and antigenic integrity of this prefusion-stabilized S.

In mice, a single sub-microgram immunization using either of the BNT162b candidates rapidly induced high antibody titres that inhibited pseudovirus entry in the range of—or above—recently reported neutralizing titres that are elicited by other candicate vaccines against SARS-CoV-2[29,30]. The candidate vaccines discussed in this Article also induced strong T_{FH} and T_H1-type $CD4^+$ T cell responses, the latter of which are thought to be a more general effect of lipid-nanoparticle-formulated modRNA vaccines against SARS-CoV-2[30]. Both $CD4^+$ T cell types are known to support antigen-specific antibody generation and maturation. In some animal models of respiratory virus infection, a T_H2-type $CD4^+$ T cell response has previously been associated with vaccine-associated enhanced respiratory disease[31,32]. Therefore, a T_H1-type response to immunization is preferred as it may reduce the theoretical risk of enhanced pulmonary disease during subsequent viral infection. Immunization with the vaccine candidates triggered redistribution of B cells from the blood to lymphoid tissues, where antigen presentation occurs. In humans, T_{FH} cells in the circulation after vaccination with a VSV-vectored Ebola vaccine candidate have previously been correlated with a high frequency of antigen-specific antibodies[33]. After vaccination of mice with BNT162b1 or BNT162b2, high numbers of T_{FH} cells were present in both the blood and lymph nodes, a potential correlate for the generation of a strong adaptive B cell response in germinal centres. In addition to eliciting favourable $CD4^+$ T cell responses, BNT162b1 and BNT162b2 both elicit $CD8^+$ T cell responses in mice, and BNT162b2 appears to be somewhat more efficient at eliciting antigen-specific cytotoxic IFNγ $CD8^+$ T cells.

BNT162b1 and BNT162b2 elicit immune profiles in macaques similar to those observed in mice. Seven days after dose 2 (of 100 μg of the candidate) was administered to macaques (during the expansion phase of the antibody response), the neutralizing GMTs elicited by either candidate reached approximately 18× the GMT of a panel of SARS-CoV-2-convalescent human sera. Neutralizing GMTs declined by day 56 (35 days after dose 2), consistent with the contraction phase; however, they remained well above the GMT of the human sera panel. The duration of the study was not long enough to assess the rate of decline during the plateau phase of the antibody response. As in mice, BNT162b2 elicted a strongly T_H1-biased $CD4^+$ T cell response and $IFN\gamma^+$ $CD8^+$ T cell response in macaques.

Limitation and clearance of virus infection is promoted by the interplay between neutralizing antibodies that eliminate infectious particles and $CD8^+$ T cells that target intracellular reservoirs of virus. $CD8^+$ T cells may also reduce the influx of monocytes into infected lung tissue, which can be associated with undesirable IL-6 and TNF production and impaired antigen presentation[34,35]. The responses elicited by the vaccine candidates reflect a pattern that is favourable for vaccine safety and efficacy, which provides added reassurance for clinical translation[36]. The contributions of the individual immune effector systems to human protection from SARS-CoV-2 are not yet understood. Therefore, it appears prudent to develop COVID-19 vaccines that enlist concomitant cognate B cell, $CD4^+$ T cell and $CD8^+$ T cell responses.

Both candidates protected 2–4-year-old macaques from challenge with infectious SARS-CoV-2, and there was reduced detection of viral RNA in immunized macaques as compared to those that received saline. Immunization with BNT162b2 provided particularly strong RT–qPCR evidence for protection of the lower respiratory tract, as demonstrated by the absence of detectable SARS-CoV-2 RNA in serial bronchoalveolar lavage samples that were obtained starting 3 days after challenge. The lack of serological response to SARS-CoV-2 challenge in BNT162b1- or BNT162b2-immunized macaques—despite a neutralizing response to challenge in control-immunized macaques—suggests suppression of infection by the vaccine candidates. Clinical signs of disease were absent, and radiological and pathological abnormalities were generally mild after challenge. As in other published reports of immunization and SARS-CoV-2 challenge of nonhuman primates, there was no evidence of vaccine-mediated enhancement of viral replication, disease or pathology[37,38]. The interpretation of vaccine-mediated protection in nonhuman primates is limited by the small number of animals and the inherent limitations of animal models. Nevertheless, these preclinical results provided key support for the immunization of large numbers of clinical-trial participants with BNT162b2.

The selection of BNT162b2 over BNT162b1 for further clinical testing was largely driven by the greater tolerability of BNT162b2 with comparable immunogenicity in clinical trials[3], and the broader range and MHC diversity of T cell epitopes on the much larger full-length S. A global phase III safety and efficacy study of immunization with BNT162b2 (NCT04368728) is ongoing, and may answer open questions that cannot be addressed by preclinical models.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information,

acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-021-03275-y.

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Methods

No statistical methods were used to predetermine sample size. The experiments were not randomized, and investigators were not blinded to allocation during experiments and outcome assessment, except for the performance of serological assays of nonhuman primates and RT–PCR-based viral load measurements and the intepretation of radiographs, computed tomography scans, and histopathology specimens.

Ethics statement

All mouse studies were performed at BioNTech SE, and protocols were approved by the local authorities (local welfare committee) and conducted according to Federation of European Laboratory Animal Science Associations recommendations. Study execution and housing were in compliance with the German Animal Welfare Act and Directive 2010/63/EU. Mice were kept in individually ventilated cages with a 12-h light/dark cycle, controlled environmental conditions (22 ± 2 °C, 45% to 65% relative humidity) and under specific-pathogen-free conditions. Food and water was available ad libitum. Only mice with an unobjectionable health status were selected for testing procedures.

Immunizations for the nonhuman primate study were performed at the University of Louisiana at Lafayette-New Iberia Research Centre (NIRC), which is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) (animal assurance no. 000452). The work was in accordance with United States Department of Agriculture Animal Welfare Act and Regulations and the NIH Guidelines for Research Involving Recombinant DNA Molecules, and Biosafety in Microbiological and Biomedical Laboratories. All procedures performed on these macaques were in accordance with regulations and established guidelines, and were reviewed and approved by an Institutional Animal Care and Use Committee or through an ethical review process. Challenge of nonhuman primates with infectious SARS-CoV-2 after immunization was performed at the Southwest National Primate Research Centre (SNPRC), Texas Biomedical Research Institute (San Antonio), which is also accredited by the AAALAC (animal assurance no. 000246). Animal husbandry followed standards recommended by AAALAC International and the NIH Guide for the Care of Use of Laboratory Animals. This study was approved by the Texas Biomedical Research Institute Animal Care and Use Committee.

Protein and peptide reagents

Purified recombinant SARS-CoV-2 RBD (Sino Biological) or trimeric S (Acro Biosystems) was used as a target for western blot, and the RBD tagged with a human Fc (Sino Biological) was used in ELISA to detect SARS-CoV-2 S-specific IgG. A recombinant SARS-CoV-2 RBD containing a C-terminal Avitag (Acro Biosystems) was used as a target antigen in Luminex immunoassays. Purified recombinant SARS-CoV-2 S1 including a histidine tag (Sino Biological) was used in ELISA to detect SARS-CoV-2 S-specific IgG in mice. Purified recombinant SARS-CoV-2 S1 and RBD with histidine tags (both Sino Biological) were used for surface plasmon resonance spectroscopy. A peptide pool of 15-mer peptides overlapping by 11 amino acids covering the full-length S was used for restimulation in ELISpot, cytokine profiling and intracellular cytokine staining followed by flow cytometry. An irrelevant peptide (SPSYVYHQF, derived from gp70 AH-1[39]) or a cytomegalovirus (CMV) peptide pool was used as control for ELISpot assays. All peptides were obtained from JPT Peptide Technologies.

Panel of SARS-CoV-2-convalescent human sera

A previously described[1–3] panel of SARS-CoV-2-convalescent human sera was used as a benchmark for nonhuman primate serology. The sera (n = 38) were drawn from donors 18–83 years of age, at least 14 days after PCR-confirmed diagnosis and at a time when the participants were asymptomatic. Most serum donors had outpatient (35/38) or inpatient (1/38) COVID-19; 2 of 38 had asymptomatic SARS-CoV-2 infections. Sera were obtained from Sanguine Biosciences, the MT Group and Pfizer Occupational Health and Wellness.

Cell culture

HEK293T and Vero 76 cells (both from ATCC) were cultured in Dulbecco's modified Eagle's medium (DMEM) with GlutaMAX (Gibco) supplemented with 10% fetal bovine serum (FBS) (Sigma-Aldrich). Cell lines were tested for mycoplasma contamination after receipt, before expansion and cryopreservation. For studies including nonhuman primate samples, Vero 76 and Vero CCL81 cells (both from ATCC) were cultured in DMEM (Gibco) containing 2% HyClone fetal bovine and 100 U ml^{-1} penicillium–streptomycin (Gibco). Expi293F cells were grown in Expi293 medium and transiently transfected using ExpiFectamine293 (all from Thermo Fisher Scientific).

In vitro transcription and purification of RNA

Antigens encoded by BNT162b vaccine candidates were designed on a background of S sequences from SARS-CoV-2 isolate Wuhan-Hu-1 (GenBank MN908947.3). The DNA template for the BNT162b1 RNA is a DNA fragment encoding a fusion protein of the SARS-CoV-2 S signal peptide (SP) (amino acids 1–16), the SARS-CoV-2 S RBD and the T4 bacteriophage fibritin trimerization motif[21] (foldon). The template for the BNT162b2 RNA is a DNA fragment encoding SARS-CoV-2 S with K986P and V987P substitutions. BNT162b1 and BNT162b2 DNA templates were cloned into a plasmid vector with backbone sequence elements (T7 promoter, 5′ and 3′ UTR, 100 nucleotide poly(A) tail) interrupted by a linker (A30LA70, 10 nucleotides) for improved RNA stability and translational efficiency[17,40]. The DNA was purified, spectrophotometrically quantified and in vitro-transcribed by T7 RNA polymerase in the presence of a trinucleotide cap1 analogue (($m_2^{7,3'\text{-O}}$)Gppp($m^{2'\text{-O}}$)ApG) (TriLink) and with N^1-methylpseudouridine-5′-triphosphate (m1ΨTP) (Thermo Fisher Scientific) replacing uridine-5′-triphosphate (UTP)[41]. RNA was purified using magnetic particles[42]. RNA integrity was assessed by microfluidic capillary electrophoresis (Agilent Fragment Analyzer), and the concentration, pH, osmolality, endotoxin level and bioburden of the solution were determined.

Lipid nanoparticle formulation of the RNA

Purified RNA was formulated into lipid nanoparticles using an ethanolic lipid mixture of ionizable cationic lipid and transferred into an aqueous buffer system via diafiltration to yield a lipid nanoparticle composition similar to one previously described[43]. The lipid nanoparticle contains RNA, an ionizable lipid, ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)), a PEGylated lipid, 2-[(polyethylene glycol)-2000]-*N*,*N*-ditetradecylacetamide and two structural lipids (1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC])and cholesterol). The vaccine candidates were stored at −70 to −80 °C at a concentration of 0.5 mg ml^{-1}.

Transfection of HEK cells

HEK293T cells were transfected with 1 μg RiboJuice transfection reagent-mixed BNT162b1 RNA or BNT162b2 RNA, or with the vaccine candidates BNT162b1 (lipid-nanoparticle-formulated BNT162b1 RNA) or BNT162b2 (lipid-nanoparticle-formulated BNT162b2 RNA) by incubation for 18 h. Non-lipid-nanoparticle-formulated mRNA was diluted in Opti-MEM medium (Thermo Fisher Scientific) and mixed with the transfection reagent according to the manufacturer's instructions (RiboJuice, Merck Millipore).

Western blot analysis of size fractions of the medium of BNT162b1-RNA-transfected cells

Medium from cultured HEK293T cells was collected. After 13-fold concentration via Vivaspin 20 centrifugal concentrators with a molecular weight cut off of 10 kDa, supernatants were applied to a preparative HiLoad 16/600 Superdex 200 pg column (both Sigma Aldrich).

The column was run at 29.8 cm h^{-1} in phosphate buffered saline (PBS), and 500-µl fractions were collected (Supplementary Fig. 1). The gel filtration column was calibrated with well-defined protein standards separated under identical conditions in a second run. Size-fractioned FBS-free medium from BNT162b1-RNA-transfected HEK293T cells was analysed by denaturing (95 °C) and non-denaturating (no heating) PAGE using 4–15% Criterion TGX Stain-Free Gel (Bio-Rad) and western blot. Transfer to a nitrocellulose membrane (Bio-Rad) was performed using a semi-dry transfer system (Trans-Blot Turbo Transfer System, Bio-Rad). Blotted proteins were detected with a monoclonal antibody that recognizes SARS-CoV-2 S1 (SinoBiological) and a secondary anti-rabbit horse radish peroxidase (HRP)-conjugated antibody (Sigma Aldrich). Blots were developed with Clarity Western ECL Substrate (Bio-Rad) and imaged with a Fusion FX Imager (Vilber) using the Image Lab software version 6.0.

Vaccine antigen detection by flow cytometry

Transfected HEK293T cells were stained with Fixable Viability Dye (eBioscience). After fixation (Fixation Buffer, Biolegend), cells were permeabilized (Perm Buffer, eBioscience) and stained with a monoclonal antibody that recognizes SARS-CoV-2 S1 (SinoBiological). Cells were acquired on a FACSCanto II flow cytometer (BD Biosciences) using BD FACSDiva software version 8.0.1 and analysed by FlowJo software version 10.6.2 (FlowJo, BD Biosciences).

Localization of expressed vaccine antigens by immunofluorescence

Transfected HEK293T cells were fixed in 4% paraformaldehyde (PFA) and permeabilized in PBS/0.2% Triton X-100. Free binding sites were blocked and cells incubated with a rabbit monoclonal antibody that recognizes the SARS-CoV-2 S1 subunit (SinoBiological), an anti-rabbit IgG secondary antibody (Jackson ImmunoResearch), labelled lectin HPA (Thermo Fisher Scientific) and concanavalin A (Fisher Scientific). DNA was stained with Hoechst (Life Technologies). Images were acquired with a Leica SP8 confocal microscope and Application Suite LAS-X Version 3.1.5.

SARS-CoV-2 RBD–foldon and S(P2) expression and purification

To express the RBD–foldon encoded by BNT162b1 for ACE2-binding analysis and cryo-EM, DNA corresponding to the RNA coding sequence was cloned into the pMCG1309 vector. A plasmid encoding amino acids 1–615 of human ACE2 with C-terminal His-10 and Avi tags was generated for transient expression of the peptidase domain of ACE2 (ACE2 PD) in Expi293F cells. The ACE2–B^0AT1 complex was produced by co-expression of two plasmids in Expi293F cells, one of them encoding ACE2 amino acids 1–17 followed by haemagglutinin and Strep II tags and ACE2 amino acids 18–805, and the other containing a methionine followed by a Flag tag and amino acids 2–634 of human B^0AT1. Secreted ACE2 PD was isolated from conditioned cell culture medium using Nickel Excel resin (GE Healthcare) followed by gel filtration chromatography on a Superdex200 10/30 column (GE Healthcare) in PBS. Approximately 5 mg of purified ACE2 PD was covalently attached per 1 ml of 4% beaded agarose by amine coupling using AminoLink Plus resin (Thermo Fisher Scientific).

The RBD trimer was purified from conditioned medium by affinity capture with the ACE2 PD crosslinked agarose and was eluted from the resin with 3 M $MgCl_2$. Following dialysis, the protein was concentrated and purified by gel filtration using a Superdex200 10/300 column in 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES)-buffered saline (HBS) with 10% glycerol. Purification of the ACE2–B^0AT1 complex was based on a previously described procedure[8]. To form the ACE2–B^0AT1–RBD-trimer complex, ACE2–B^0AT1 aliquots were combined with purified RBD–foldon diluted in size-exclusion chromatography buffer (25 mM Tris pH 8.0, 150 mM NaCl, 0.02% glyco diosgenin) for a 3:1 molar ratio of RBD trimers to ACE2 protomers. After incubation at 4 °C for 30 min, the sample was concentrated and resolved on a Superose 6 Increase 10/300 GL column. Peak fractions containing the complex were pooled and concentrated.

To express SARS-CoV-2 S(P2) encoded by BNT162b2 for characterization by size-exclusion chromatography, ACE2-PD binding, monoclonal antibody binding and cryo-EM, a gene encoding the full length of SARS-CoV-2 (GenBank MN908947) with two prolines substituted at residues 986 and 987 (K986P and V987P) followed with a C-terminal HRV3C protease site and a TwinStrep tag was cloned into a modified pcDNA3.1(+) vector with the CAG promoter. The TwinStrep-tagged S(P2) was expressed in Expi293F cells.

Purification of the recombinant protein was based on a previously described procedure, with minor modifications[9]. Upon cell lysis, S(P2) was solubilized in 1% NP-40 detergent. The TwinStrep-tagged protein was then captured with StrepTactin Sepharose HP resin in 0.5% NP-40. S(P2) was further purified by size-exclusion chromatography and eluted as three distinct peaks in 0.02% NP-40, as previously reported[9] (chromatogram not shown). A peak that consists of intact S(P2) migrating at around 150 kDa, as well as dissociated S1 and S2 subunits (which co-migrate at just above 75 kDa), was used in the structural characterization. Spontaneous dissociation of the S1 and S2 subunits occurs throughout the course of protein purification, starting at the point of detergent-mediated protein extraction, so that S(P2) preparations also contain dissociated S1 and S2.

Binding kinetics of the RBD–foldon trimer and S(P2) to immobilized human ACE2 and a neutralizing monoclonal antibody by biolayer interferometry

Binding of purified RBD–foldon to ACE2 PD and of NP-40 solubilized, purified S(P2) to ACE2 PD and human neutralizing monoclonal antibody B38[25] was measured by biolayer interferometry at 25 °C on an Octet RED384 (FortéBio). RBD–foldon binding was measured in 10 mM HEPES pH 7.5, 150 mM NaCl and 1 mM EDTA (EDTA). S(P2) binding was measured in 25 mM Tris pH 7.5, 150 mM NaCl, 1 mM EDTA and 0.02% NP-40. Avi-tagged human ACE2 PD was immobilized on streptavidin-coated sensors; B38 antibody was immobilized on protein G-coated sensors. For an RBD–foldon concentration series, binding data were collected for 600 s of association and 900 s of dissociation. For an S(P2) concentration series, after initial baseline equilibration of 120 s, the sensors were dipped in a 10 µg ml^{-1} solution of Avi-tagged ACE2 PD or B38 monoclonal antibody for 300 s to achieve capture levels of 1 nM using the threshold function. Then, after another 120 s of baseline, binding data were collected for 300 s of association and 600 s of dissociation.

Biolayer interferometry data were collected with Octet Data Acquisition software version 10.0.0.87 and processed using ForteBio Data Analysis software version 10.0. Data were reference-subtracted and fit to a 1:1 binding model with R^2 value greater than 0.96 for the RBD and 0.95 for S(P2). Potential avidity effects for the RBD–foldon and potential ongoing dissociation of S1 from S(P2) could make the actual binding events more complicated than represented by 1:1 binding model. Therefore, we report apparent kinetics and affinity (S(P2)) or avidity (RBD–foldon) of binding as calculated using Octet Data Analysis Software v.10.0 (FortéBio). For the RBD–foldon, the dissociation rate of interaction (k_d) with ACE2 PD was slower than the limit of measurement of the instrument, and the apparent minimum binding avidity (K_D) was estimated using an assumed dissociation rate k_d of 1×10^{-6} s^{-1}.

Electron microscopy of negatively stained RBD–foldon trimers

Purified RBD–foldon in 4 µl was applied to a glow-discharged copper grid overlaid with formvar and amorphous carbon (Ted Pella). Negative staining was performed with Nano-W organotungstate stain (Nanoprobes) according to the manufacturer's protocol. The sample imaged using an FEI TF-20 microscope operating at 200 kV, with a magnification of 62,000× and defocus of −2.5 µm. Micrographs were contrast transfer function (CTF)-corrected in RELION using CTFFIND-4.1[44]. A

small manually picked dataset was used to generate 2D references for autopicking. The resulting particle set was subjected to 2D classification in RELION 3.0.6[45].

Cryo-EM of the ACE2–B^{0}AT1–RBD-trimer complex

Cryo-EM was performed using a Titan Krios operating at 300 keV equipped with a Gatan K2 Summit direct electron detector in super-resolution mode at a magnification of 165,000×, for a magnified pixel size of 0.435 Å at the specimen level.

Purified ACE2–B^{0}AT1–RBD-trimer complex at 6 mg ml^{-1} in 4 µl was applied to gold Quantifoil R1.2/1.3 200 mesh grids glow-discharged in residual air for 30 s at 20 mA using a Pelco Easiglow. The sample was blotted using a Vitrobot Mark IV for 5 s with a force of −3 before being plunged into liquid ethane cooled by liquid nitrogen. In total, 7,455 micrographs were collected from a single grid. Data were collected over a defocus range of −1.2 to −3.4 µm with a total electron dose of 52.06 e$^-$ per Å^2 fractionated into 40 frames over a 6-s exposure for 1.30 e$^-$ per Å^{2}per frame. Initial motion correction was performed in Warp[46], during which super-resolution data were binned to give a pixel size of 0.87 Å. Corrected micrographs were imported into RELION 3.1-beta[45] for CTF estimation with CTFFIND-4.1[44].

Particles were picked using the LaPlacian-of-Gaussian particle-picking algorithm as implemented in RELION, and extracted with a box size of 450 pixels. References obtained by 2D classification were used for a second round of reference-based autopicking, yielding a dataset of 715,356 particles. Two of the three RBDs of each particle (the two not constrained by binding to ACE2–B^{0}AT1) exhibited diffuse density in 2D classification that reflected high particle flexibility, consistent with the conformational flexibility of RBD trimers observed by negative-stain electron microscopy (Fig. 1c, d). This flexibility precluded the inclusion of all three RBDs in the final structural solution. Particle heterogeneity was filtered out with 2D and 3D classification with a mask size of 280 Å to filter out the diffuse density of the two non-ACE2-bound RBD copies in each RBD trimer, yielding a set of 87,487 particles that refined to 3.73 Å with C2 symmetry. Refinement after subtraction of micelle and B^{0}AT1 density from the particles yielded an improved map of 3.24 Å. The atomic model from Protein Data Bank code (PDB) 6M17[8] was rigid-body-fitted into the 3.24 Å density and then flexibly fitted to the density using real-space refinement in Phenix[47] alternating with manual building in Coot[48]. The microscope was operated for image acquisition using SerialEM software version 3.8.0 beta[49]. Validation of this model is shown in Supplementary Fig. 2. Data collection, 3D reconstruction and model refinement statistics are listed in Extended Data Table 1.

Cryo-EM of S(P2)

For TwinStrep-tagged S(P2), 4 µl purified protein at 0.5 mg ml^{-1} were applied to gold Quantifoil R1.2/1.3 300 mesh grids freshly overlaid with graphene oxide. The sample was blotted using a Vitrobot Mark IV for 4 s with a force of −2 before being plunged into liquid ethane cooled by liquid nitrogen. We collected 27,701 micrographs from 2 identically prepared grids. Data were collected from each grid over a defocus range of −1.2 to −3.4 µm with a total electron dose of 50.32 and 50.12 e$^-$ per Å^2, respectively, fractionated into 40 frames over a 6-s exposure for 1.26 and 1.25 e$^-$ per Å^2 per frame. On-the-fly motion correction, CTF estimation, and particle-picking and extraction with a box size of 450 pixels were performed in Warp[46], during which super-resolution data were binned to give a pixel size of 0.87 Å. A total of 1,119,906 particles were extracted. All subsequent processing was performed in RELION 3.1-beta[45]. Particle heterogeneity was filtered out with 2D and 3D classification, yielding a set of 73,393 particles that refined to 3.6 Å with C3 symmetry. Three-dimensional classification of this dataset without particle alignment separated out one class with a single RBD up, representing 15,098 particles. The remaining 58,295 particles, in the three-RBD-down conformation, were refined to give a final model at 3.29 Å. The atomic model from PDB 6XR8[9] was rigid-body fitted into the map density, then flexibly fitted to the density using real-space refinement in Phenix[47] alternating with manual building in Coot[48]. The cryo-EM model validation is provided in Extended Data Fig. 2, and the full cryo-EM data processing workflow and the model refinement statistics in provided in Extended Data Table 1.

Immunization

Mice. Female BALB/c mice (Janvier) (8–12 weeks old) were randomly allocated to groups. BNT162b1 and BNT162b2 diluted in PBS with 300 mM sucrose (Fig. 2a–c, Extended Data Figs. 3 for both BNT162 vaccine candidates; Fig. 2e, Extended Data Fig. 4a for BNT162b2) or 0.9% NaCl (Fig. 2d, Extended Data Fig. 4b–e for both BNT162 vaccine candidates; Fig. 2e, Extended Data Fig. 4a for BNT162b1) were injected into the gastrocnemius muscle at a volume of 20 µl under isoflurane anaesthesia. PBS with 300 mM sucrose or 0.9% NaCl served as buffer controls, respectively.

Macaques. Male macaques (2–4 years old) were randomly assigned to receive BNT162b1 or BNT162b2 on days 0 and 21 or saline control on days 0 and 21 or 35. Vaccine was administered in 0.5 ml by intramuscular injection in the left quadriceps muscle. Macaques were anaesthetized with ketamine HCl (10 mg kg^{-1}; intramuscular) during immunization and were monitored for adequate sedation.

Phlebotomy and tissue preparation

Mice. Peripheral blood was collected from the retro-orbital venous plexus under isoflurane anaesthesia or the vena facialis without anaesthesia. For flow cytometry, blood was heparinized. For serum generation, blood was centrifuged for 5 min at 16,000*g* and the serum was immediately used for downstream assays or stored at −20 °C. Spleen single-cell suspensions were prepared in PBS by mashing tissue against the surface of a 70-µm cell strainer (BD Falcon). Erythrocytes were removed by hypotonic lysis. Popliteal, inguinal and iliac lymph nodes were pooled, cut into pieces, digested with collagenase D (1 mg ml^{-1}) (Roche) and passed through cell strainers.

Macaques. Serum was obtained before, 6 h after and 1, 14, 21, 28, 35 and 42 days after injection with BNT162b1, BNT162b2 or saline (Extended Data Table 2). For BNT162b2 and challenge cohort 3 controls, serum was also obtained on day 56, and peripheral blood mononuclear cells (PBMCs) were obtained before immunization and on days 7, 28, and 42 (except that PBMCs were not obtained from the challenge cohort 3 control macaques on day 28). Blood for serum and PBMCs was collected in compliance with animal protocol 2017-8725-023, approved by the NIRC Institutional Animal Care and Use Committee. Macaques were anaesthetized with ketamine HCl (10 mg kg^{-1}; intramuscular) during blood collection and were monitored for adequate sedation.

Analysis of S1- and RBD-specific serum IgG

Mice. MaxiSorp plates (Thermo Fisher Scientific) were coated with recombinant S1 or RBD (1 µg ml^{-1}) in sodium carbonate buffer, and serum-derived bound IgG was detected using an HRP-conjugated secondary antibody and tetramethylbenzidine substrate (Biotrend). Data collection was performed using a BioTek Epoch reader and Gen5 software version 3.0.9. For concentration analysis, an IgG mouse isotype control was used in parallel in a serial dilution, and the sample signals were correlated to a standard curve of the isotype control.

Macaques and humans. Recombinant SARS-CoV-2 S1 containing a C-terminal Avitag (Acro Biosystems) was bound to streptavidin-coated Luminex microspheres. Bound macaque or human anti-S1 antibodies present in the serum were detected with a fluorescently labelled goat anti-human polyclonal secondary antibody (Jackson ImmunoResearch). Data were captured as median fluorescent intensities using a Bioplex200 system (Bio-Rad) and converted to U ml^{-1} antibody concentrations using a reference standard consisting of 5

pooled SARS-CoV-2-convalescent human serum samples (obtained >14 days after PCR diagnosis, from the panel described in 'Panel of SARS-CoV-2-convalescent human sera'), diluted in antibody-depleted human serum with arbitrary assigned concentrations of 100 U ml^{-1} and accounting for the serum dilution factor.

Surface plasmon resonance spectroscopy of polyclonal mouse immune sera

Binding kinetics of mouse S1- and RBD-specific serum IgG to recombinant S1 and RBD was determined using a Biacore T200 device (Cytiva) with 10 mM HEPES, 150 mM NaCl, 3 mM EDTA, 0.05% v/v surfactant P20 (HBS-EP running buffer, BR100669, Cytiva) at 25 °C. Carboxyl groups on the CM5 sensor chip matrix were activated with a mixture of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimidehydrochloride and *N*-hydroxysuccinimide to form active esters for the reaction with amine groups. Anti-mouse IgG Fc-antibody (Jackson ImmunoResearch) was diluted in 10 mM sodium acetate buffer pH 5 (30 µg ml^{-1}) for covalent coupling to immobilization level of about 10,000 response units. Free *N*-hydroxysuccinimide esters on the sensor surface were deactivated with ethanolamine.

Mouse serum was diluted 1:50 in HBS-EP buffer and applied at 10 µl min^{-1} for 30 s to the active flow cell for capture by immobilized antibody, and the reference flow cell was treated with buffer. Binding analysis of captured mouse IgG antibodies to S1–His or RBD–His (Sino Biological) was performed using a multicycle kinetic method with concentrations ranging from 25 to 400 nM or 1.56 to 50 nM, respectively. An association period of 180 s was followed by a dissociation period of 600 s with a constant flow rate of 40 µl min^{-1} and a final regeneration step. Apparent binding kinetics for the captured polyclonal IgG were calculated using a global kinetic fit model (1:1 Langmuir, Biacore T200 Evaluation Software Version 3.1, Cytiva).

VSV-SARS-CoV-2 S pseudovirus entry-inhibition assay by serum IgG in mice

A recombinant replication-deficient VSV vector that encodes green fluorescent protein (GFP) instead of VSV-G (VSV(ΔG–GFP)) was pseudotyped with SARS-CoV-2 S according to published pseudotyping protocols[50,51]. In brief, HEK293T/17 monolayers transfected to express SARS-CoV-2 S truncated of the C-terminal cytoplasmic 19 amino acids (SARS-CoV-2-S(CΔ19)) were inoculated with VSVΔG-GFP vector (rescued from pVSVΔG-GFP plasmid expression vector; Kerafast). After incubation for 1 h at 37 °C, the inoculum was removed, and cells were washed with PBS before medium supplemented with anti-VSV-G antibody (clone 8G5F11, Kerafast) was added to neutralize residual input virus. VSV-SARS-CoV-2 pseudovirus-containing medium was collected 20 h after inoculation, 0.2-µm-filtered and stored at −80 °C.

Vero-76 cells were seeded in 96-well plates. Serial dilutions of mouse serum samples were prepared and pre-incubated for 10 min at room temperature with VSV-SARS-CoV-2 pseudovirus suspension (4.8×10^3 infectious units per ml) before transferring the mix to Vero-76 cells. Inoculated Vero-76 cells were incubated for 20 h at 37 °C. Plates were placed in an IncuCyte Live Cell Analysis system (Sartorius) and incubated for 30 min before the analysis (IncuCyte 2019B Rev2 software). Whole-well scanning for bright-field and GFP fluorescence was performed using a 4× objective. The $pVNT_{50}$ is reported as the reciprocal of the highest dilution of serum that still yielded a 50% reduction in GFP-positive infected cell number per well, compared to the mean of the no-serum pseudovirus positive control. Each serum sample dilution was tested in duplicate.

IFNγ and IL-4 ELISpot

Mice. ELISpot assays were performed with mouse IFNγ ELISpot^{PLUS} kits according to the manufacturer's instructions (Mabtech). A total of 5×10^5 splenocytes was ex vivo restimulated with the full-length S peptide mix (0.1 µg ml^{-1} final concentration per peptide) or controls (gp70-AH1 (SPSYVYHQF)[39], 4 µg ml^{-1}; concanavalin A, 2 µg ml^{-1} (Sigma)). Streptavidin–alkaline phosphatase and 5-bromo-4-chloro-3′-indolyl phosphate/nitro blue tetrazolium-plus substrate were added, and spots counted using an ELISpot plate reader (ImmunoSpot S6 Core Analyzer (CTL)). Spot numbers were evaluated using ImmunoCapture Image Acquisition Software v.7.0 and ImmunoSpot 7.0.17.0 Professional. Spot counts denoted too numerous to count by the software were set to 1,500. For T cell subtyping, $CD8^+$ T cells and $CD4^+$ T cells were isolated from splenocyte suspensions using MACS MicroBeads (CD8a (Ly-2) and CD4 (L3T4) (Miltenyi Biotec)) according to the manufacturer's instructions. $CD8^+$ or $CD4^+$ T cells (1×10^5) were subsequently restimulated with 5×10^4 syngeneic bone-marrow-derived dendritic cells loaded with full-length S peptide mix (0.1 µg ml^{-1} final concentration per peptide), or cell culture medium as control. The purity of isolated T cell subsets was determined by flow cytometry to calculate spot counts per 1×10^5 $CD8^+$ or $CD4^+$ T cells.

Macaques. Macaque PBMCs were tested with commercially available nonhuman primate IFNγ and IL-4 ELISpot assay kits (Mabtech). Cryopreserved macaque PBMCs were thawed in prewarmed AIM-V medium (Thermo Fisher Scientific) with benzonase (EMD Millipore). For IFNγ ELISpot, 1.0×10^5 PBMCs, and for IL-4 ELISpot, 2.5×10^5 PBMCs, were stimulated ex vivo with 1 µg ml^{-1} of the full-length S overlapping peptide mix. Tests were performed in triplicate wells and medium containing dimethyl sulfoxide (medium–DMSO), a CMV peptide pool and phytohemagglutinin (Sigma) were included as controls. After 24 h for IFNγ and 48 h for IL-4, streptavidin–HRP and 3-amino-9-ethylcarbazole substrate (BD Bioscience) were added and spots counted using a CTL ImmunoSpot S6 Universal Analyzer (CTL). Results shown are background (medium–DMSO) subtracted and normalized to spot-forming cells per 10^6 PBMCs.

Cell-mediated immunity by flow cytometry

Mice. For T cell analysis in peripheral blood, erythrocytes from 50 µl freshly drawn blood were lysed (ammonium–chloride–potassium lysing buffer (Gibco)), and cells were stained with Fixable Viability Dye (eBioscience) and primary antibodies in the presence of Fc block in flow buffer (Dulbecco's phosphate-buffered saline (Gibco) supplemented with 2% fetal calf serum (FCS), 2 mM EDTA (both Sigma) and 0.01% sodium azide (Morphisto)). After staining with secondary biotin-coupled antibodies in flow buffer, cells were stained extracellularly against surface markers with directly labelled antibodies and streptavidin in Brilliant Stain Buffer Plus (BD Bioscience) diluted in flow buffer. Cells were washed with 2% RotiHistofix (Carl Roth), fixed (Fix/Perm Buffer, FoxP3/Transcription Factor Staining Buffer Set (eBioscience)) and permeabilized (Perm Buffer, FoxP3/Transcription Factor Staining Buffer Set (eBioscience)) overnight. Permeabilized cells were intracellularly treated with Fc block and stained with antibodies against transcription factors in Perm Buffer.

For T cell analysis in lymphoid tissues, 1×10^6 lymph node cells (for BNT162b1) or 1.5×10^6 lymph node cells (for BNT162b2) and 4×10^6 spleen cells were stained for viability and extracellular antigens with directly labelled antibodies. Fixation, permeabilization and intracellular staining was performed as described for blood T cell staining.

For B cell subtyping in lymphoid tissues, 2.5×10^5 lymph node and 1×10^6 spleen cells were treated with Fc block, stained for viability and extracellular antigens as described for blood T cell staining, and fixed with 2% RotiHistofix overnight.

For intracellular cytokine staining of T cells from BNT162b1-immunized mice, 1×10^6 lymph node and 4×10^6 spleen cells were ex vivo restimulated with 0.2 µg ml^{-1} final concentration per peptide of full-length S peptide mix. For intracellular cytokine staining of T cells from mice immunized using BNT162b2, 4×10^6 spleen cells were ex vivo restimulated with 0.5 µg ml^{-1} final concentration per peptide of full-length S peptide mix or cell culture medium (no peptide) as control.

The cells were restimulated for 5 h in the presence of GolgiStop and GolgiPlug (both BD Bioscience) for 5 h. Cells were stained for viability and extracellular antigens as described for lymphoid T cell staining. Cells were fixed with 2% RotiHistofix and permeabilized overnight. Intracellular staining was performed as described for blood T cell staining.

Mouse cells were acquired on a BD Symphony A3 or BD Celesta (B cell subtyping) flow cytometer (BD Bioscience) using BD FACSDiva software version 9.1 or 8.0.1.1, respectively, and analysed with FlowJo 10.6 (FlowJo, BD Biosciences).

Macaques. For intracellular cytokine staining in T cells, 1.5×10^6 PBMCs were stimulated with the full-length S peptide mix at 1 μg ml^{-1} (concentration of all peptides, combined), *Staphyloccocus* enterotoxin B (2 μg ml^{-1}) as positive control, or 0.2% DMSO as negative control. GolgiStop and GolgiPlug (both BD Bioscience) were added. Following 37-°C incubation for 12 to 16 h, cells were stained for viability and extracellular antigens after blocking Fc binding sites with directly labelled antibodies. Cells were fixed, permeabilized with BDCytoFix/CytoPerm solution (BD Bioscience), and intracellular staining was performed in the permeabilization buffer for 30 min at room temperature. Cells were washed, resuspended in 2% FBS/PBS buffer and acquired on an LSR Fortessa. Data were analysed by FlowJo 10.4.1 (FlowJo, BD Biosciences). Results shown are background (medium–DMSO) subtracted.

Cytokine profiling in mice by bead-based immunoassay

Mouse splenocytes were restimulated for 48 h with full-length S peptide mix (0.1 μg ml^{-1} final concentration per peptide) or cell culture medium (no peptide) as control. Concentrations of IFNγ, IL-2, IL-4, IL-5 and (for splenocytes from BNT162b2-immunized mice) IL-13 in supernatants were determined using a bead-based, 11-plex T_H1/T_H2 mouse ProcartaPlex multiplex immunoassay (Thermo Fisher Scientific) according to the manufacturer's instructions. Fluorescence was measured with a Bioplex200 system (Bio-Rad) and analysed with ProcartaPlex Analyst 1.0 software (Thermo Fisher Scientific). Values below the lower limit of quantification were set to zero.

SARS-CoV-2 neutralization by macaque sera

The SARS-CoV-2 neutralization assay used a previously described strain of SARS-CoV-2 (USA_WA1/2020) that had been rescued by reverse genetics and engineered by the insertion of an mNeonGreen gene into open reading frame 7 of the viral genome[27]. This reporter virus generates similar plaque morphologies and indistinguishable growth curves from wild-type virus. Viral master stocks were grown in Vero E6 cells as previously described[52]. When testing human convalescent serum specimens, the fluorescent neutralization assay produced comparable results to the conventional plaque reduction neutralization assay. Serial dilutions of heat-inactivated sera were incubated with the reporter virus (2×10^4 plaque forming units (PFU) per well) to yield an approximately 10–30% infection rate of the Vero CCL81 monolayer for 1 h at 37 °C before inoculating Vero CCL81 cell monolayers (targeted to have 8,000 to 15,000 cells in the central field of each well at the time of seeding, one day before infection) in 96-well plates to allow accurate quantification of infected cells. Cell counts were enumerated by nuclear stain (Hoechst 33342), and fluorescent virus-infected foci were detected 16–24 h after inoculation with a Cytation 7 Cell Imaging Multi-Mode Reader (BioTek) with Gen5 Image Prime version 3.09. Titres were calculated in GraphPad Prism version 8.4.2 by generating a 4-parameter logistical fit of the per cent neutralization at each serial serum dilution. The VNT_{50} is reported as the interpolated reciprocal of the dilution yielding a 50% reduction in fluorescent viral foci.

SARS-CoV-2 challenge of macaques

The SARS-CoV-2 inoculum was obtained from a stock of 2.1×10^6 PFU ml^{-1} previously prepared at Texas Biomedical Research Institute, aliquoted into single-use vials and stored at −70 °C. The working virus stock was generated from two passages of the SARS-CoV-2 USA-WA1/2020 isolate (a fourth passage seed stock purchased from BEI Resources; NR-52281) in Vero E6 cells. The virus was confirmed to be SARS-CoV-2 by deep sequencing that demonstrated identity to a published SARS-CoV-2 sequence (GenBank accession number MN985325.1).

BNT162b1-immunized ($n = 6$) and BNT162b2-immunized ($n = 6$) male macaques, and age-matched male macaques mock-immunized with saline ($n = 9$) (control), were challenged with 1.05×10^6 PFU of SARS-CoV-2 USA-WA1/2020 isolate, split equally between the intranasal (0.25 ml) and intratracheal (0.25 ml) routes, as previously described[28]. Sentinel age- and sex-matched macaques ($n = 6$) were mock-challenged with DMEM supplemented with 10% FCS intranasally (0.25 ml) and intratracheally (0.25 ml). The macaques were challenged or mock-challenged at the times relative to immunization indicated in Extended Data Fig. 6, Extended Data Table 2.

Twelve to nineteen days before challenge, macaques were moved from the NIRC where they had been immunized to the animal biosafety level 3 facility at SNPRC. Macaques were monitored regularly by a board-certified veterinary clinician for rectal body temperature, weight and physical examination. Specimen collection was performed under tiletamine zolazepam (Telazol) anaesthesia as previously described[28]. Bronchoalveolar lavage, and nasal, oropharyngeal and rectal swab collection, X-ray and CT examinations and necropsy were performed at the times indicated in Extended Data Fig. 6, Extended Data Table 2. The three control macaques in challenge cohort 3 and three sentinel macaques were not necropsied to allow their subsequent rechallenge (control) or challenge (sentinel). Bronchoalveolar lavage was performed by instilling 20 ml of saline 4 times. These washings were pooled, aliquoted and stored frozen at −70 °C.

SARS-CoV-2 viral RNA quantification by RT–qPCR

To detect and quantify SARS-CoV-2 in nonhuman primates, viral RNA was extracted from bronchoalveolar lavage fluid and from nasal, oropharyngeal and rectal swabs as previously described[53–55], and tested by RT–qPCR as previously described[28]. In brief, 10 μg yeast tRNA and 1×10^3 PFU of MS2 phage (*Escherichia coli* bacteriophage MS2) (ATCC) were added to each thawed sample, and RNA extraction performed using the NucleoMag Pathogen kit (Macherey-Nagel). The SARS-CoV-2 RT–qPCR was performed on extracted RNA using a 2019-nCoV N1 assay developed by the United States Centers for Disease Control and Prevention, on a QuantStudio 3 instrument (Applied Biosystems). The cut-off for positivity (limit of detection) was established at 10 gene equivalents per reaction (800 gene equivalents per ml). Samples were tested in duplicate. One bronchoalveolar lavage specimen from the challenge cohort 2 control group obtained on day 6 after challenge, and one nasal swab from the BNT162b1-immunized group obtained on day 1 after challenge, had—on repeated measurements—viral RNA levels on either side of the LLOD. These specimens were categorized as indeterminate and excluded from the graphs and the analysis.

Radiology

Thoracic radiographs and computed tomography scans were performed under anaesthesia, as previously described[28]. For radiographic imaging, three-view thoracic radiographs (ventrodorsal, right and left lateral) were obtained at the times relative to challenge indicated in Extended Data Table 2. The macaques were anaesthetized using telazol (2–6 mg kg^{-1}) and maintained by inhaled isoflurane delivered through a Hallowell 2002 ventilator anaesthesia system (Hallowell). Macaques were intubated to perform end inspiratory breath-hold using a remote breath-hold switch. Lung field computed tomography images were acquired using Multiscan LFER150 PET/CT (MEDISO) scanner. Image analysis was performed using 3D region-of-interest tools available in Vivoquant (Invicro). Images were interpreted by a board-certified veterinary radiologist blinded to treatment groups. Scores were assigned to a total of 7 lung regions on a severity scale of 0–3 per region, with

a maximum severity score of 21. Pulmonary lesions evident before challenge, or those which could not be unequivocally attributed to the viral challenge (such as atelectasis secondary to recumbency and anaesthesia), received a score of 0.

Histopathology

Lung histopathology is reported on necropsies performed on 2–4-year-old male macaques at the times after challenge indicated in Extended Data Fig. 6, Extended Data Table 2. Necropsy, tissue processing and histology were performed by SNPRC. Samples were fixed in 10% neutral buffered formalin and processed routinely into paraffin blocks. Tissue blocks were sectioned to 5 µm and stained with haematoxylin and eosin. Microscopic evaluation of 7 lung tissue sections per macaque (1 sample of each lobe in the left and right lungs) was performed blindly by SNPRC and Pfizer pathologists. Lungs were evaluated using a semiquantitative scoring system with inclusion of cell types and/or distribution as appropriate. Inflammation score was based on area of tissue in section involved: 0 = normal; 1 ≤ 10%; 2 = 11–30%; 3 = 30–60%; 4 = 60–80%; 5 ≥ 80%. Each lobe received an individual score, and the final score for each macaque was reported as the mean of the individual scores. The pathologists were unblinded to the group assignments after agreement on diagnoses. As indicated in Extended Data Fig. 6, Extended Data Table 2, the BNT162b1-immunized and control macaques were challenged and necropsied in parallel (challenge cohorts 1 and 2), and the BNT162b2-immunized macaques were immunized and challenged subsequently (challenge cohort 3).

Statistics and reproducibility

No statistical methods were used to predetermine group and samples sizes (*n*). All experiments were performed once. *P* values reported for RT–qPCR analysis were determined by nonparametric analysis (Friedman's test) based on the ranking of viral RNA shedding data within each day. PROC RANK and PROC GLM from SAS 9.4 were used to calculate the *P* values. All available post-challenge bronchoalveolar lavage fluid and nasal, oropharyngeal and rectal swab samples from the necropsied macaques and all available post-challenge samples through day 10 from the macaques that were not necropsied were included in the analysis. Indeterminate results were excluded from this analysis. All remaining analyses were two-tailed and carried out using GraphPad Prism 8.4.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this paper.

Data availability

The SARS-CoV-2 isolate Wuhan-Hu-1 (GenBank MN908947.3) is the genetic background of the BNT162b antigens. The cryo-EM maps and atomic coordinates have been deposited to the Electron Microscopy Data Bank (EMDB) and PDB with accession numbers EMD-23211 and 7L7F, respectively, for the ACE2–B^0AT1–RBD–foldon complex and EMD-23215 and 7L7K, respectively, for S(P2). The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions U.S. conceived and conceptualized the work and strategy. S.Hein, S.C.D., A.A.H.S., C.K., R.d.l.C.G.G., and M.C.G. designed primers, performed oligosynthesis, cloned constructs and performed protein expression experiments. T.Z., S.F., J.S. and A.N.K. developed, planned, performed and supervised RNA synthesis and analysis. E.H.M. purified S(P2). N.L.N. purified RBD trimer and ACE2 peptidase domain. J.A.L. developed ACE2–B^0AT1–RBD trimer formation and purified the complex. P.V.S. developed and performed biolayer interferometry experiments. J.A.L. and S. Han performed electron microscopy and solved the structure of the complex. Y.C. supervised the structural and biophysical characterization and analysed the structures. A.M. and B.G.L. performed surface plasmon resonance spectroscopy. A.G., S.A.K., S.S., T.H., L.F. and F.V. planned, performed and analysed in vitro studies. F.B., T.K. and C.R. managed the formulation strategy. A.B.V., M.V., L.M.K. and K.C.W. designed mouse studies, and analysed and interpreted data. A.P., S.E., D.P. and G.S. performed and analysed the S1- and RBD-binding IgG assays. M.G. designed and optimized MS2 SARS-nCoV-2 N1 RT–qPCR assay. M.G., R.C. Jr and K.J.A. performed and analysed viral RT-qPCR data. A.M., B.S. and A.K.-W. performed and analysed pVNT assays. C.F.-G. and P.-Y.S. performed and analysed VNT assays. D.E., D.S., B.J., Y.F. and H.J. performed in vivo studies and ELISpot assays. A.B.V., K.C.W., J.L., M.S.M., A.O.-S. and M.V. planned, analysed and interpreted ELISpot assays. L.M.K., J.L., D.E., Y.F., H.J., A.P.H., M.S.M. and P.A.-Q. planned, performed and analysed flow cytometry assays. A.B.V., L.M.K., Y.F. and H.J. planned, performed, analysed and interpreted cytokine release assays. M.R.G. read and interpreted radiographs and computed tomography scans. O.G. and S.C. read and interpreted histopathology specimens. R.S.S. and S.C. interpreted histopathology data. I.K., K.A.S., K.T., C.Y.T., M.G., D.K. and P.R.D. designed nonhuman primate studies, and analysed and interpreted data. K.T., M.P., I.L.S. and W.V.K. oversaw immunogenicity and serology testing of nonhuman primates. S.H.-U. and K.B. provided veterinary services for nonhuman primates. J.A.F., J.C., T.C. and J.O. managed the nonhuman primate colony. U.S., Ö.T., P.R.D, L.M.K., A.M. and M.V. contributed to synthesis and integrated interpretation of obtained data. A.B.V., I.K., Y.C., A.M., M.V., L.M.K., C.T., K.A.S., Ö.T., P.R.D, K.U.J. and U.S. wrote the manuscript. All authors supported the review of the manuscript.

Competing interests The authors declare that U.S. and Ö.T. are management board members and employees at BioNTech SE (Mainz, Germany); K.C.W., B.G.L., D.S., B.J., T.H., T.K. and C.R. are employees at BioNTech SE; A.B.V., A.M., M.V., L.M.K., S. Hein, A.G., T.Z., F.B., A.P., D.E., S.C.D., S.F., S.E., F.B., B.S., A.K.-W., Y.F., H.J., S.A.K., S.S., A.P.H., P.A.-Q., J.S., A.A.H.S., C.K., R.d.l.C.G.G., L.F. and A.N.K. are employees at BioNTech RNA Pharmaceuticals GmbH (Mainz, Germany);

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Additional information

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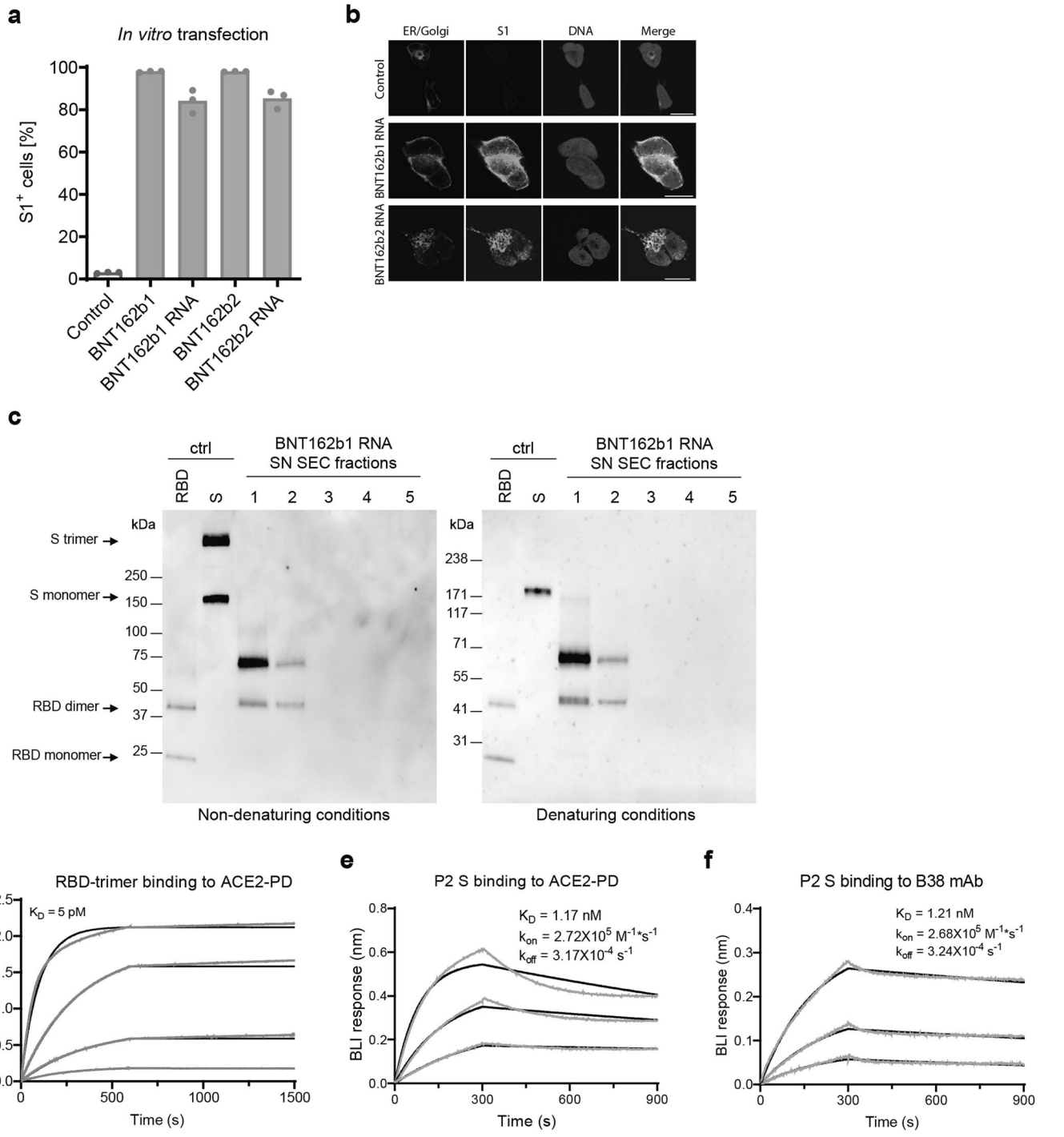
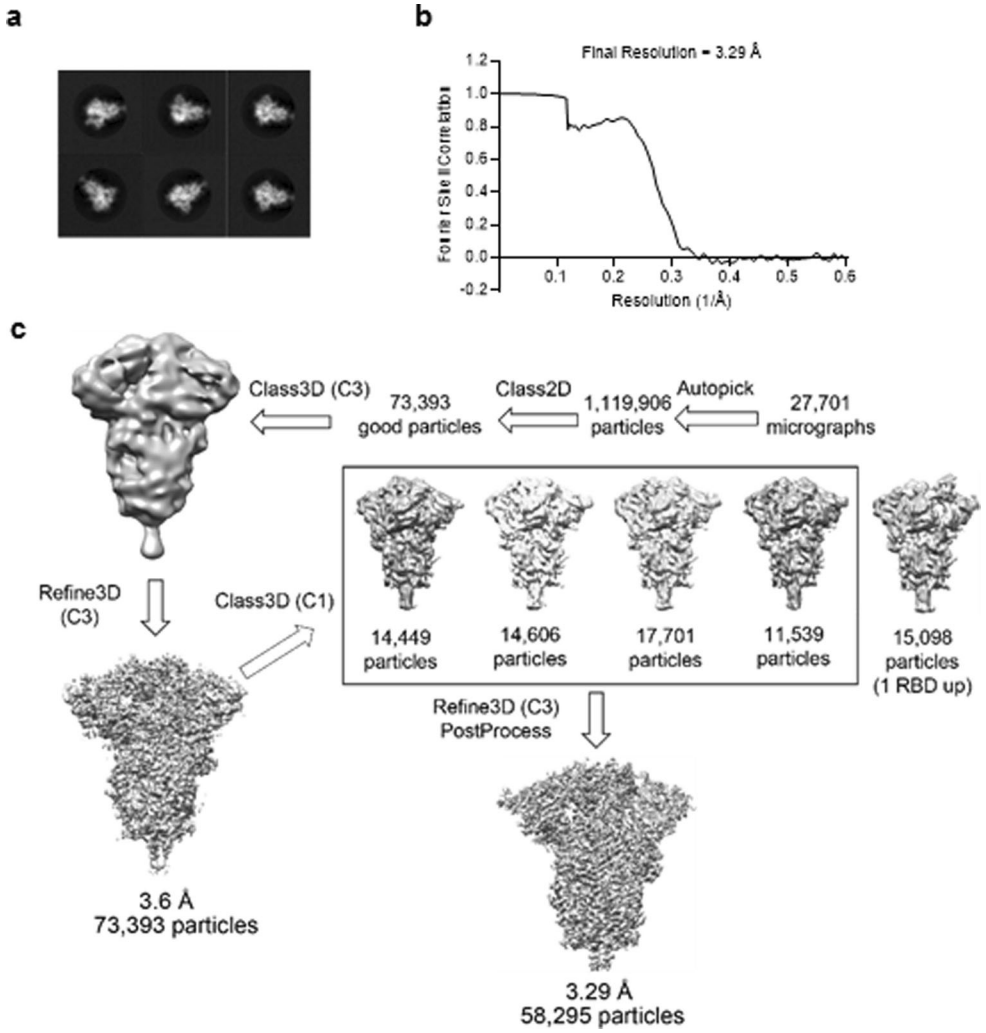
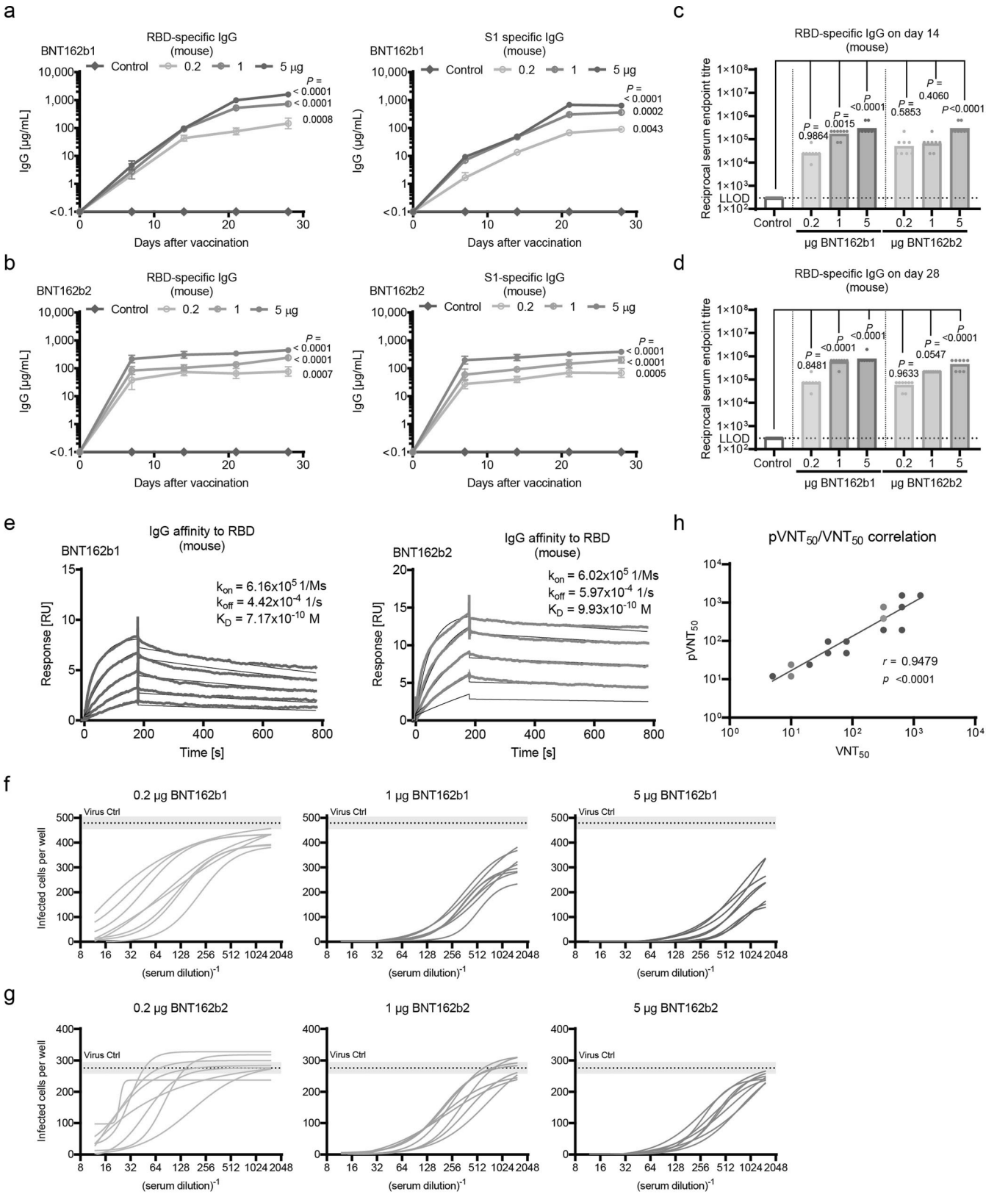


Extended Data Fig. 1 | Antigen expression and receptor affinity of vaccines. **a**, Detection of BNT162b1-encoded RBD–foldon and BNT162b2-encoded S(P2) in HEK293T cells by S1-specific antibody staining and flow cytometry. HEK293T cells analysed by flow cytometry were incubated with: no RNA (control), BNT162b RNA formulated as lipid nanoparticles (BNT162b1 and BNT162b2) or BNT162b RNAs mixed with a transfection reagent (BNT162b1 RNA and BNT162b2 RNA). Heights of bars indicate the means of technical triplicates. **b**, Localization of BNT162b1 RNA-encoded RBD–foldon or BNT162b2 RNA-encoded S(P2) in HEK293T cells transfected as in **a**, determined by immunofluorescence staining. Endoplasmic reticulum and Golgi (ER/Golgi) (red), S1 (green) and DNA (blue). Scale bar, 10 µm. **c**, Western blot of denatured and non-denatured samples of size-exclusion chromatography fractions (chromatogram in Supplementary Fig. 1) of concentrated medium from HEK293T cells transfected with BNT162b1 RNA. The RBD–foldon was detected with a rabbit monoclonal antibody against the S1 fragment of SARS-CoV-2 S. Protein controls (ctrl): purified, recombinant RBD and S. **d**, Biolayer interferometry (BLI) sensorgram demonstrating the binding kinetics of the purified RBD–foldon trimer, expressed from DNA, to immobilized human ACE2 PD. **e**, **f**, Biolayer inferometry sensorgrams showing binding of a DNA-expressed S(P2) preparation from a size-exclusion chromatography peak (not shown) that contains intact S(P2) and dissociated S1 and S2 to immobilized human ACE2 PD (**e**) and B38 monoclonal antibody (**f**). Binding data are in colour; 1:1 binding models fit to the data are in black. Apparent kinetic parameters are provided in the graphs.

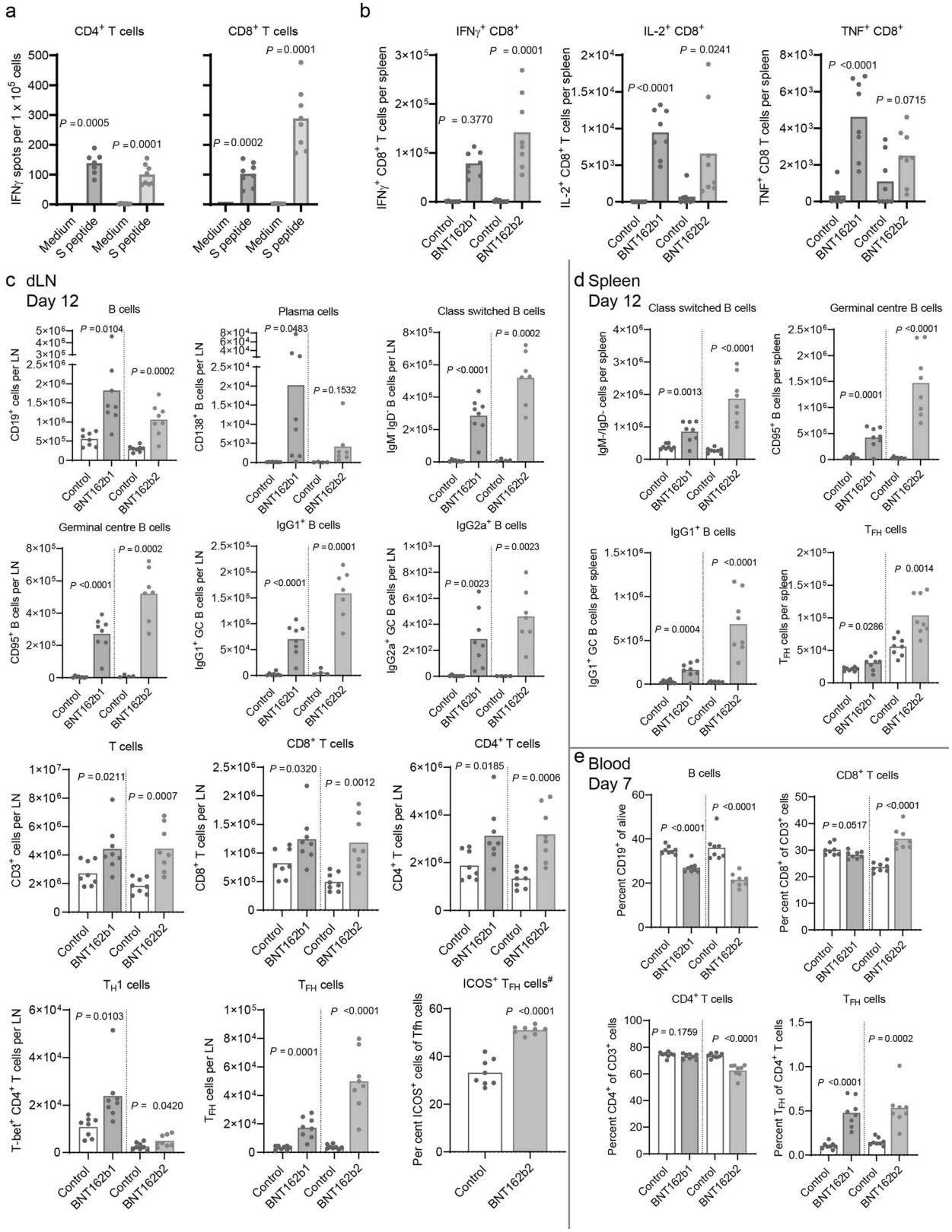


Extended Data Fig. 2 | Cryo-EM evidence for alternative conformers of S(P2). a, Representative 2D class averages of TwinStrep-tagged S(P2) particles extracted from cryo-EM micrographs. Box edge, 39.2 nm. **b**, Fourier shell correlation curve from RELION gold-standard refinement of the S(P2) trimer. **c**, Flowchart for cryo-EM data processing of the complex, showing 3D class averages.



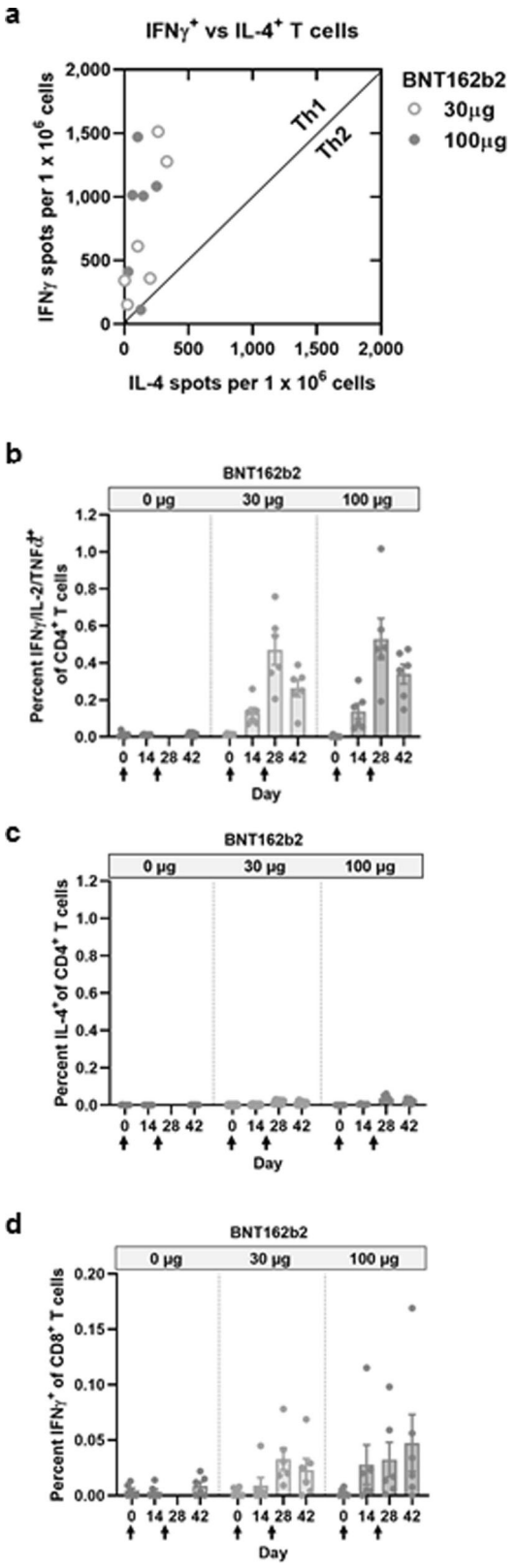
Extended Data Fig. 3 | See next page for caption.

Extended Data Fig. 3 | BNT162b-elicited antibody responses in mice. **a**–**d**, BALB/c mice ($n = 8$) were injected intramuscularly with a single dose of one of the BNT162b vaccine candidate or buffer (control, $n = 8$ (**a**, **b**) and $n = 16$ (**c**, **d**)). *P* values of day 28 compared to control (multiple comparison of mixed-effect analysis (**a**, **b**) and one-way analysis of variance (**c**, **d**), all using Dunnett's multiple comparisons test) are provided. **a**, **b**, RBD- and S1-specific IgG responses (geometric mean of each group ± 95% confidence interval) in sera obtained 7, 14, 21 and 28 days after injection with BNT162b1 (**a**) or BNT162b2 (**b**), determined by ELISA. For day-0 values, a prescreening of randomly selected mice was performed ($n = 4$). **c**, **d**, RBD-specific IgG reciprocal serum endpoint titres 14 (**c**) and 28 days (**d**) after injection. The horizontal dotted line indicates the LLOD. Each data point represents one mouse, and the height of bar indicates the geometric mean of groups. **e**, **f**, Representative surface plasmon resonance sensorgram of the binding kinetics of His-tagged RBD (**e**) to immobilized mouse IgG from serum drawn 28 days after injection with 5 µg BNT162b candidates. Binding data (in colour) and 1:1 binding model fit to the data (black) are depicted. **e**, Number of infected cells per well in a VSV-SARS-CoV-2 $pVNT_{50}$ assay conducted with serial dilutions of mouse serum samples drawn 28 days after injection with BNT162b1 (**f**) or BNT162b2 (**g**). Lines represent individual sera measured in triplicate. Horizontal dotted lines indicate geometric mean ± 95% confidence interval (as grey area) of infected cells in the absence of mouse serum (virus-positive control). **h**, Pearson correlation of VSV-SARS-CoV-2 $pVNT_{50}$ with live SARS-CoV-2 VNT_{50} for $n = 10$ random selected serum samples from mice immunized with BNT162b1 and BNT162b2 each. For several samples, identical $pVNT_{50}$ and VNT_{50} values were measured: blue symbols represent individual mice; red symbols represent 2 mice; green symbol represents 3 mice.



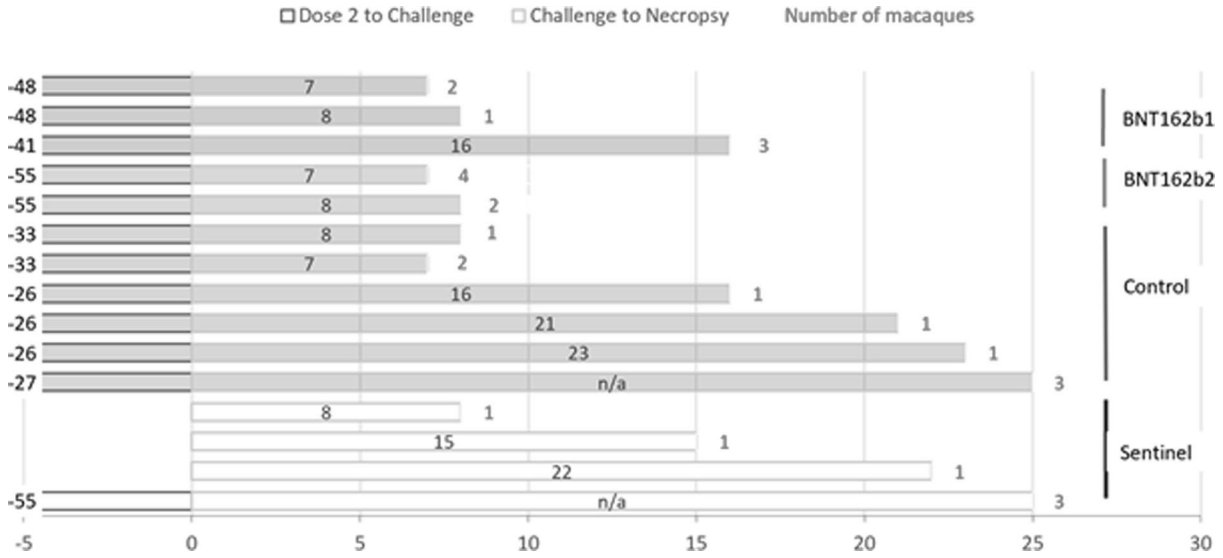
Extended Data Fig. 4 | See next page for caption.

Extended Data Fig. 4 | T cell response and T cell and B cell phenotyping of BNT162b-immunized mice. BALB/C mice ($n = 8$ per group, unless stated otherwise) were injected intramuscularly with one of the BNT162b vaccines or buffer (control). **a**, **b**, Separated T cells from spleen or splenocytes of BALB/c mice were ex vivo restimulated with full-length S peptide mix or cell culture medium (medium). Symbols represent individual mice. Height of bars indicate the mean of each group. **a**, IFNγ ELISpot of separated splenic $CD4^+$ or $CD8^+$ T cells after immunization using 1 µg of one of the BNT162b vaccines (BNT162b1, $n = 7$ for $CD4^+$ T cells, one outlier removed by Grubbs test, $\alpha = 0.05$). *P* values compare immunized groups with the control (parametric, two-tailed paired *t*-test). **b**, $CD8^+$ T-cell-specific cytokine release by splenocytes after immunization using 5 µg of one of the BNT162b vaccines or buffer (control), determined by flow cytometry. S-peptide-specific responses are corrected for background (medium). *P* values compare immunized groups with the control (parametric, two-tailed unpaired *t*-test assuming equal s.d.). **c**–**e**, T cell and B cell phenotype composition after immunization with BNT162b candidates was determined by flow cytometry. *P* values were determined by a two-tailed, unpaired *t*-test assuming populations to have the same s.d. **c**, B cell and T cell numbers in draining lymph nodes (dLN) (popliteal, iliac and inguinal lymph nodes). For B cell subtyping, control, $n = 4$; BNT162b2, $n = 7$. [#]For per cent $ICOS^+$ cells of T_{FH} cells, only BNT162b2 data are available. **d**, B cell and T_{FH} cell numbers in the spleen. **e**, B cell and T cell numbers in the blood.

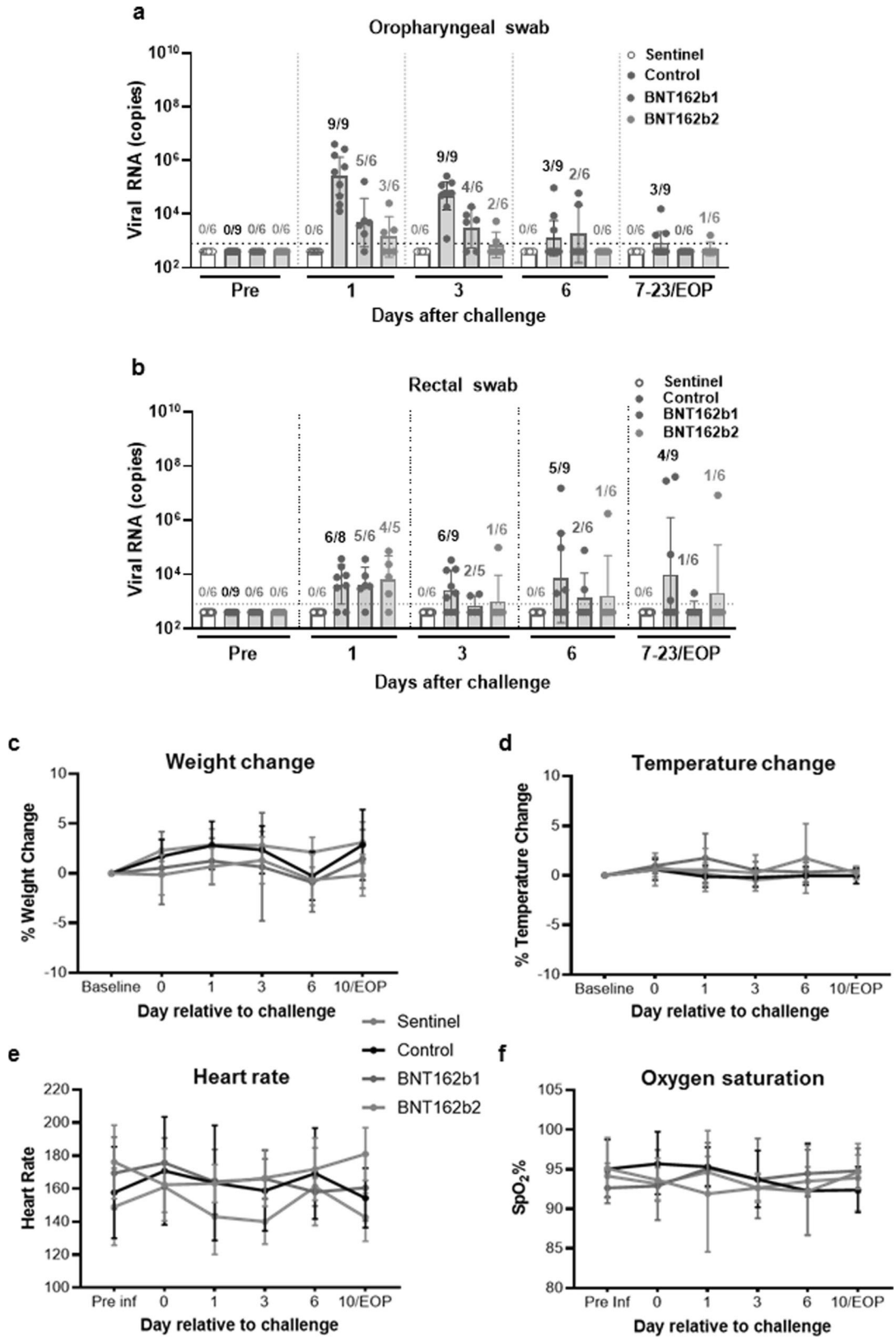


Extended Data Fig. 5 | See next page for caption.

Extended Data Fig. 5 | Macaque $CD4^+$ and $CD8^+$ T cell response. Macaques ($n = 6$ per group) were injected on day 0 and day 21 with 30 µg or 100 µg BNT162b2, as in Figs. 3, 4. PBMCs collected on days 0, 14, 28 and 42 after BNT162b2 injection were ex vivo restimulated with full-length S peptide mix. **a**, Scatter plot showing the correlation of IL-4- and IFNγ-secreting cells by ELISpot of day-42 PBMCs. **b**, IFNγ, IL-2 or TNF release from $CD4^+$ T cells by flow cytometry (LLOD = 0.04). **c**, IL-4 release from $CD4^+$ T cells by flow cytometry (LLOD = 0.05). **d**, IFNγ release from $CD8^+$ T cells by flow cytometry (LLOD = 0.03). Heights of bars indicate the arithmetic means for each group. Whiskers indicate s.e.m. (**b**–**d**). Each symbol represents one macaque. Horizontal dashed lines mark LLODs. Values below the LLOD were set to 1/2 the LLOD. Arrows below the *x* axis indicate the days of doses 1 and 2.

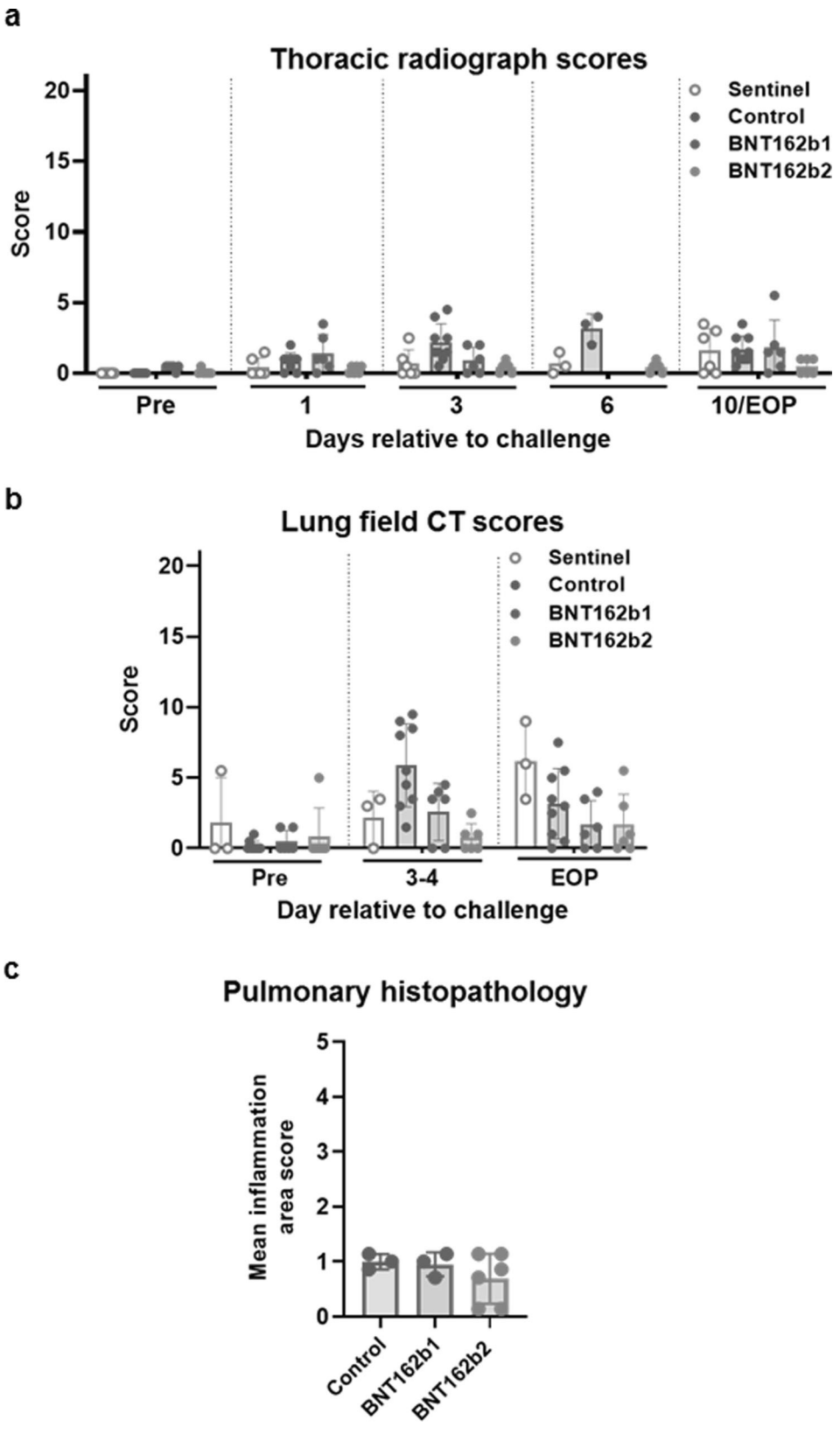


Extended Data Fig. 6 | Schedule of macaque SARS-CoV-2 challenge and necropsy. Timing in days from dose 2 of vaccine or saline (numbers to the left of the bars) and of necropsy (numbers inside bars) are presented relative to the day of SARS-CoV-2 or mock-challenge (day 0). Numbers of macaques represented by the bars are indicated by red numbers to the right of the bars. Control, macaques challenged but not immunized with BNT162b. Sentinel, macaques mock-challenged (cell culture medium only). n/a, macaques not necropsied. Additional details, including timing of sample collections and radiographic examinations, are in Extended Data Table 2.



Extended Data Fig. 7 | See next page for caption.

Extended Data Fig. 7 | Viral RNA detection in oropharyngeal and rectal swabs, and clinical signs in BNT162b-immunized macaques after challenge with infectious SARS-CoV-2. Macaques immunized using 100 μg of BNT162b1 or BNT162b2 ($n = 6$ each) and macaques mock-immunized using saline or not immunized (control, $n = 9$) (as described in Fig. 4, Extended Data Fig. 6, Extended Data Table 2) were challenged with 1.05×10^6 total PFU of SARS-CoV-2 split equally between the intranasal and intratracheal routes. Additional macaques (sentinel, $n = 6$) were mock-challenged with cell culture medium. **a**, **b**, Viral RNA levels were detected by RT–qPCR in oropharyngeal (**a**) and rectal (**b**) swabs. Ratios above data points indicate the number of viral-RNA-positive macaques among all macaques that provided evaluable samples in a group. Heights of bars indicate geometric mean of viral RNA copies; whiskers indicate geometric s.d. Every symbol represents one macaque. Dotted lines indicate the LLODs. Values below the LLOD were set to 1/2 the LLOD. The two-sided statistical significance by Friedman's nonparametric test of differences in viral RNA detection between 6 BNT162b1-immunized and 6 contemporaneously control-immunized macaques (challenge cohorts 1 and 2) after challenge was $P < 0.0001$ for oropharyngeal swabs and $P = 0.1179$ for rectal swabs; between 6 BNT162b2-immunized macaques and 3 contemporaneously control-immunized macaques (challenge cohort 3) after challenge, the statistical significance was $P = 0.0007$ for oropharyngeal swabs and $P = 0.2209$ for rectal swabs. **c**–**f**, Vital signs were recorded. **c**, Body weight change. **d**, Temperature change. **e**, Heart rate. **f**, Oxygen saturation. Each data point represents an arithmetic mean. Whiskers indicate s.d.



Extended Data Fig. 8 | See next page for caption.

Extended Data Fig. 8 | Radiographic signs and pulmonary histopathology of macaques immunized with BNT162b1 or BNT162b2 and challenged with SARS-CoV-2. Macaques were immunized using BNT162b1 or BNT162b2 or mock-immunized with saline (control) and challenged with SARS-CoV-2, and a sentinel group was challenged with cell culture medium. The disposition of the macaques for immunization, infectious challenge, imaging and necropsy are described in Figs. 3, 4, Extended Data Fig. 6, Extended Data Table 2. Three-view thoracic radiographs (ventrodorsal, right and left lateral) and lung field computed tomography images were obtained. The macaques were anaesthetized and intubated to perform end inspiratory breath-hold. Images were interpreted by two board-certified veterinary radiologists blinded to treatment groups. Scores were assigned to 7 lung regions on a severity scale of 0–3 per region, with a maximum severity score of 21. Pulmonary lesions evident before challenge, or those which could not be unequivocally attributed to the viral challenge (such as atelectasis secondary to recumbency and anaesthesia), received a score of 0. **a**, Thoracic radiograph scores. **b**, Lung field computed tomography scores. Each dot represents the summed radiograph or computed tomography scores for the seven lung lobes of a single macaque. Two veterinary pathologists blindly performed microscopic evaluation of formalin-fixed, haematoxylin and eosin-stained lung tissue sections from each of seven lobes from each macaque that had been necropsied on day 7 or day 8. Inflammation scores were assigned by consensus between the pathologists on a scale of 1–5 on the basis of the area of involvement. **c**, Pulmonary histopathology scores. Each dot represents the mean inflammation area score from the seven lung lobes of an individual macaque. In **a**–**c**, the height of each bar indicates the arithmetic mean of the radiograph, computed tomography or histopathology score, respectively, for the macaques in each group, and whiskers indicate s.d.

Extended Data Table 1 | Cryo-EM data collection, 3D reconstruction and refinement statistics

Data collection	ACE2/B^{0}AT1/RBD complex	P2 S	
Electron microcsopy equipment	Titan Krios (Thermo Fisher Scientific)		
Voltage (keV)	300		
Detector	K2 Summit		
Energy filter	Gatan GIF, 20 eV slit		
Nominal magnification	165,000 x		
Pixel size (Å)	0.435 (super-resolution)		
		Grid 1	**Grid 2**
Electron dose (e^-/Å^2)	52.06	50.32	50.12
Dose rate (e-/Å^2/sec)	8.7	8.4	8.33
Defocus range (μm)	-1.2 to -3.4	-1.2 to -3.4	-1.2 to -3.4
Number of collected micrographs	7455	10,422	17,279
Number of selected micrographs	7372	27701	
3D reconstruction			
	ACE2/B^{0}AT1/RBD	**ACE2/RBD focused**	
Software	Relion	Relion	Warp, Relion
Number of used particles	74,784	74,784	58,295
Symmetry imposed	C2	C2	C3
Global resolution (Å)			
Fourier shell correlation=0.143	3.73	3.24	3.29
Applied B factor (Å^2)	-100	-79.8	-50
Refinement			
Software		Phenix, Coot	Phenix, Coot
Protein residues		1,788	2,919
Map correlation coefficient		0.86	0.78
Root mean square deviation			
Bond length (Å)		0.005	0.003
Bond angles (°)		1.021	0.610
Ramachandran plot statistics (%):			
Preferred		91.7	94.6
Allowed		8.3	5.4
Outlier		0	0
Poor rotamers (%)		0.25	7.06
MolProbity score		1.88	2.51
EMRinger score		2.76	2.23
Clashscore (all atoms)		6.98	9.41

Extended Data Table 2 | Schedule of macaque immunization, challenge, sample collection, radiological examination and necropsy

Challenge group[1]	Immunization[2]	DOB	Serum collection relative to immunization	Pre challenge serum collection (week after Dose 1)	Challenge cohort[3]	Days between Dose 2 and challenge (if applicable)[4]	Sample collections relative to challenge					Necropsy day (post challenge)
							Nasal, oral, rectal swab	Chest X-ray	Chest CT	BAL	Serum	
BNT162b1	BNT162b1 100 µg	5/3/2017	Pre, 6h, 24h, W1, 2, 3, 4, 5, 6	8	2	48	pre/1/3/6/7	pre/1/3/7	pre/3/7	pre/3/6/7	pre/3/6/7	7
BNT162b1	BNT162b1 100 µg	5/20/2016	Pre, 6h, 24h, W1, 2, 3, 4, 5, 6	8	2	48	pre/1/3/6/7	pre/1/3/7	pre/3/7	pre/3/6/7	pre/3/6/7	7
BNT162b1	BNT162b1 100 µg	5/20/2016	Pre, 6h, 24h, W1, 2, 3, 4, 5, 6	8	2	48	pre/1/3/6/8	pre/1/3/8	pre/3/8	pre/3/6/8	pre/3/6/8	8
BNT162b1	BNT162b1 100 µg	5/17/2016	Pre, 6h, 24h, W1, 2, 3, 4, 5, 6	8	1	41	pre/1/3/6/9/16	pre/1/3/16	pre/3/16	pre/3/6/16	pre/3/6/16	16
BNT162b1	BNT162b1 100 µg	5/17/2016	Pre, 6h, 24h, W1, 2, 3, 4, 5, 6	8	1	41	pre/1/3/6/9/16	pre/1/3/16	pre/3/16	pre/3/6/16	pre/3/6/16	16
BNT162b1	BNT162b1 100 µg	5/6/2016	Pre, 6h, 24h, W1, 2, 3, 4, 5, 6	8	1	41	pre/1/3/6/9/16	pre/1/3/16	pre/3/16	pre/3/6/16	pre/3/6/16	16
BNT162b2	BNT162b2 100 µg	5/19/2017	Pre, 6h, 24h, W1, 2, 3, 4, 5, 6, 8	10	3	55	pre/1/3/6/7	pre/1/3/6/7	pre/3/7	pre/3/6/7	pre/3/6/7	7
BNT162b2	BNT162b2 100 µg	5/19/2017	Pre, 6h, 24h, W1, 2, 3, 4, 5, 6, 8	10	3	55	pre/1/3/6/7	pre/1/3/6/7	pre/3/7	pre/3/6/7	pre/3/6/7	7
BNT162b2	BNT162b2 100 µg	6/1/2017	Pre, 6h, 24h, W1, 2, 3, 4, 5, 6, 8	10	3	55	pre/1/3/6/7	pre/1/3/6/7	pre/3/7	pre/3/6/7	pre/3/6/7	7
BNT162b2	BNT162b2 100 µg	6/14/2017	Pre, 6h, 24h, W1, 2, 3, 4, 5, 6, 8	10	3	55	pre/1/3/6/7	pre/1/3/6/7	pre/3/7	pre/3/6/7	pre/3/6/7	7
BNT162b2	BNT162b2 100 µg	5/18/2017	Pre, 6h, 24h, W1, 2, 3, 4, 5, 6, 8	10	3	55	pre/1/3/6/8	pre/1/3/6/8	pre/3/8	pre/3/6/8	pre/3/6/8	8
BNT162b2	BNT162b2 100 µg	5/19/2017	Pre, 6h, 24h, W1, 2, 3, 4, 5, 6, 8	10	3	55	pre/1/3/6/8	pre/1/3/6/8	pre/3/8	pre/3/6/8	pre/3/6/8	8
Control	Saline	5/17/2017	Pre, 6h, 24h, W1, 2, 3, 4, 5, 6	8	2	33	pre/1/3/4/6/7	pre/1/3/4/7	pre/4/7	pre/3/6/7	pre/3/6/7	7
Control	Saline	4/19/2017	Pre, 6h, 24h, W1, 2, 3, 4, 5, 6	8	2	33	pre/1/3/4/6/7	pre/1/3/4/7	pre/4/7	pre/3/6/7	pre/3/6/7	7
Control	Saline	7/12/2016	Pre, 6h, 24h, W1, 2, 3, 4, 5, 6	8	2	33	pre/1/3/6/8	pre/1/3/8	pre/3/8	pre/3/6/8	pre/3/6/8	8
Control	Saline	5/20/2016	Pre, 6h, 24h, W1, 2, 3, 4, 5, 6	8	1	26	pre/1/3/6/9/16	pre/1/3/16	pre/3/16	pre/3/6/16	pre/3/6/16	16
Control	Saline	3/30/2016	Pre, 6h, 24h, W1, 2, 3, 4, 5, 6	8	1	26	pre/1/3/6/9/21	pre/1/3/21	pre/3/21	pre/3/6/21	pre/3/6/21	21
Control	Saline	6/7/2016	Pre, 6h, 24h, W1, 2, 3, 4, 5, 6	8	1	26	pre/1/3/6/9/23	pre/1/3/23	pre/3/23	pre/3/6/23	pre/3/6/23	23
Control	Saline	5/22/2017	Pre, 6h, 24h, W1, 2, 3	6	3	27	pre/1/3/6/10	pre/1/3/6/10	pre/3/10	pre/3/6	pre/3/6/10	not necropsied
Control	Saline	6/12/2017	Pre, 6h, 24h, W1, 2, 3	6	3	27	pre/1/3/6/10	pre/1/3/6/10	pre/3/10	pre/3/6	pre/3/6/10	
Control	Saline	5/29/2017	Pre, 6h, 24h, W1, 2, 3	6	3	27	pre/1/3/6/10	pre/1/3/6/10	pre/3/10	pre/3/6	pre/3/6/10	
Sentinel	-	3/27/2016	-	-	2	-	pre/1/3/4/6/8	pre/1/3/4/8	pre/4/8	pre/3/6/8	pre/3/6/8	8
Sentinel	-	6/5/2017	-	-	1	-	pre/1/3/6/9/15	pre/1/3/4/15	pre/3/15	pre/3/6/15	pre/3/6/15	15
Sentinel	-	5/30/2017	-	-	1	-	pre/1/3/6/9/22	pre/1/3/4/22	pre/3/22	pre/3/6/22	pre/3/6/22	22
Sentinel	BNT162b2 30 µg	5/18/2017	Pre, 6h, 24h, W1, 2, 3, 4, 5, 6, 8	10	3	55	pre/1/3/6/10	pre/1/3/6/10	10	pre/3/6	pre/3/6/10	not necropsied
Sentinel	BNT162b2 30 µg	5/27/2017	Pre, 6h, 24h, W1, 2, 3, 4, 5, 6, 8	10	3	55	pre/1/3/6/10	pre/1/3/6/10	10	pre/3/6	pre/3/6/10	
Sentinel	BNT162b2 30 µg	6/9/2017	Pre, 6h, 24h, W1, 2, 3, 4, 5, 6, 8	10	3	55	pre/1/3/6/10	pre/1/3/6/10	10	pre/3/6	pre/3/6/10	

[1]All macaques in the BNT162b1, BNT162b2 and control challenge groups were challenged with SARS-CoV-2. Macaques in the sentinel challenge group were mock-challenged.
[2]'No immunization' is indicated by '–'.
[3]Challenge cohort 2 was challenged with SARS-CoV-2 or mock-challenged one week after challenge cohort 1. Challenge cohort 3 was challenged with SARS-CoV-2 or mock-challenged six weeks after challenge cohort 2.
[4]All macaques were challenged with SARS-CoV-2 or mock-challenged, according to their challenge group. The entry for 'days from dose 2 to SARS-COV-2 or mock challenge' for macaques that were not immunized is '–'.

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☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
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☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
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Software and code

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Data collection	Western Blot: Fusion FX Imager (Vilber), Image Lab software version 6.0 Flow cytometry data: BD Biosciences, BD FACSDiva V9.1 or 8.0.1 Immunofluorescence: Leica SP8 confocal microscope, Application Suite LAS-X Version 3.1.5.16308 Biolayer interferometry: Octet Data Acquisition software version 10.0.0.87, ForteBio Data Analysis software version 10.0 Cryo-EM: Titan Krios (Thermo Fisher Scientific), SerialEM software version 3.8.0 beta S1- and RBD-binding IgG assay data; Cytokine profiling: Gen5 V3.0.9 or Bioplex200 system (Bio-Rad), Surface plasmon resonance spectroscopy: Biacore T200 device (Cytiva), Biacore T200 Evaluation Software Version 3.1 pVNT: IncuCyte Live Cell Analysis system (Sartorius), IncuCyte 2019B Rev2 software ELISPOT spot count data: ImmunoSpot® S6 Core Analyzer or Universal Analyzer [CTL], Image Aquision V7.0 or the ImmunoSpot 7.0.17.0 Professional VNT: Cell Imaging Multi-Mode Reader (BioTek), Gen5 Image Prime version 3.09 RT-qPCR: QuantStudio 3 instrument (Applied Biosystems)
Data analysis	Flow cytometry: FlowJo V10.6 or 10.4.1 (FlowJo LLC, BD Biosciences) Biolayer interferometry: Octet Data Analysis v10.0 (FortéBio) Cryo-EM: RELION 3.1-beta Cytokine profiling: ProcartaPlex Analyst 1.0 software (Thermo Fisher Scientific) Data visualisation and statistical analysis: GraphPad Prism V8

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The data that support the findings of this study are available from the corresponding author upon reasonable request.
The vaccine sequence is based on GenBank: MN908947.3
For P2 S, the atomic model from PDB ID 6XR8 was rigid-body fitted into the map density (https://www.rcsb.org/structure/6XR8).
The cryo-EM maps and atomic coordinates have been deposited to the Electron Microscopy Data Bank (EMDB) and Protein Data Bank (PDB) with accession numbers EMD-23211 and PDB 7L7F for the ACE2/B0AT1/RBD-foldon complex and EMD-23215 and PDB 7L7K for P2 S.

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No sample-size calculation was performed. For mouse studies, a two-sided test with the hypothesis that the mean is a given value, with the shift to be detected a multiple of the standard deviation was taken into account. For α=0.05 and a desired power of 80%, a group size of n = 8 is required to find significant differences between groups. For non-human primate studies, sample size was limited by availability of suitable animals.
Data exclusions	No data was excluded.
Replication	Replication was not attempted. Independent studies and analysis methods to analyse immune responses were performed.
Randomization	Mice or NHP were randomly allocated to groups. No formal randomization was done.
Blinding	Studies were performed unblinded as analyis results could not be manipulated by interpretation. Thoracic radiographs and computed tomography scan images were interpreted by a board-certified veterinary radiologist blinded to treatment groups. Histopathology slides were read by veterinary pathologists blinded to treatment groups.

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☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☐	☒ Human research participants
☐	☒ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	Used reagents (specificity/ fluorochrome/ clone/ manufacturer/ catalogue number/lot number/dilution): Anti-mouse: B220/CD45R / AF647 / RA3-6B2 / BioLegend / 103226 / B243962 / 1:1500

CD138 / BV605 / 281-2 / BioLegend / 142531 / B299222 / 1:200
CD19 / BV786 / 1D3 / BD Bioscience / 563333 / 0023948 / 1:1000
CD19 / AF700 / 6D5 / BioLegend / 115528 / B261756 / 1:100
CD278/ICOS / PerCPeF710 / 7E.17G9 / Invitrogen / 46-9942-82 / 2029789 / 1:50
CD38 / PE / 90 / eBioscience / 12-0381-82 / 2150667 / 1:400
CD38 / AF488 / 90 / BioLegend / 102714 / B298187 / 1:100
CD3e / BUV395 / 145-2C11 / BD Bioscience / 563565 / 9204644 / 1:100
CD4 / PerCP-Cy5.5 / RM4-5 / BioLegend / 100540 / B261856 / 1:800
CD4 / BV480 / RM4-5 / BD Bioscience / 565634 / 9016508, 0107454 / 1:250
CD44 / BUV563 / IM7 / BD Bioscience / 741227 / 0119427 / 1:5000, 1:2500
CD62L / BV785 / MEL-14 / BioLegend / 104440 / B258213 / 1:200
CD8a / PerCP-Cy5.5 / 53-6.7 / BD Bioscience / 551162 / 9098816 / 1:800
CD8a / BUV737 / 53-6.7 / BD Bioscience / 564297 / 9030634 / 1:200
CD8a / FITC / 53-6.7 / BD Bioscience / 553031 / 9143776 / 1:200
CD95/Fas / FITC / Jo2 / BD Bioscience / 561979 / 8296755 / 1:100
CXCR5 / Purified / 2G8 / BD Bioscience / 551961 / 9143926 / 1:100
CXCR5 / BV421 / L138D7 / BioLegend / 145512 / B281252 / 1:100
F4/80 / PerCP-Cy5.5 / BM8 / BioLegend / 123128 / B276793 / 1:800
FC block CD16/CD32 / Purified / 2.4G2 / BD Bioscience / 553142 / 9060742 / 1:100
GATA3 / PE-Cy7 / TWAJ / Invitrogen / 25-9966-42 / 2142972 / 1:25
GR-1 / PerCP-Cy5.5 / RB6-8C5 / BioLegend / 108428 / B278340 / 1:800
IFNγ / PE-Cy7 / XMG1.2 / BD Bioscience / 564336 / 9337390 / 1:1000
IgD / BV421 / 11-26c.2a / BioLegend / 405725 / B280598 / 1:2500
IgG1 / BV480 / A85-1 / BD Bioscience / 746811 / 0115095 / 1:200
IgG2a / BV711 / R19-15 / BD Bioscience / 744533 / 0115092 / 1:200
IgG2a / Biotin / RG7/1.30 / BD Bioscience / 553894 / 9288614 / 1:100
IgM (Igh-Ca/Cb) / PE-Cy7 / R6-60.2 / BD Bioscience / 552867 / 9269114 / 1:200
IL-2 / APC-R700 / JES6-5H4 / BD Bioscience / 565186 / 9303906 / 1:5000
PD-1/CD279 / BV605 / 29F.1A12 / BioLegend / 135219 / B303691 / 1:50
T-bet / AF647 / 4B10 / bioLegend / 644804 / B248741 / 1:200
TNF / BB700 / MP6-XT22 / BD Bioscience / 566510 / 0021825 / 1:5000

Anti-rhesus, anti-human:
CD154 / BV605 / 24-31 / BioLegend / 310826 / B250362 / 1:60
CD20 / PE-Cy5.5 / 2H7 / Invitrogen / 35-0209-41 / 2005219 / 1:600
CD3 / AF700 / SP34-2 / BD Bioscience / 557917 / 9277122 / 1:15
CD4 / BF480 / SK3 / BD Bioscience / 566104 / 58964 / 1:60, 1:30
CD8 / BB700 / RPA-T8 / BD Bioscience / 566452 / 16984 / 1:1200
IFNγ / FITC / B27 / BD Bioscience / 552887 / 9329760 / 1:15
IL-2 / PE-Cy7 / MQ1-17H12 / Invitrogen / 25-7029-42 / 2136515 / 1:60
IL-4 / BV421 / MP4-25D2 / BD Bioscience / 564110 / 15834 / 1:30
TNF / BUV395 / Mab11 / BD Bioscience / 563996 / 10280 / 1:30
TruStain FcX / Purified / - / BioLegend / 422302 / B298875 / 1:60

Anti-viral:
SARS-CoV-2 (2019-nCoV) Spike Antibody, Rabbit Mab / AF647 (labelled) / #007 / Sino Biological / 40150-R007 / MA14FE2702 / 1:400 [flow cytometry]
SARS-CoV-2 (2019-nCoV) Spike Antibody, Rabbit Mab / Purified / #007 / Sino Biological / 40150-R007 / MA14FE2702 / 1:1000 [Western blot]
SARS-CoV-2 (2019-nCoV) Spike Antibody, Rabbit Mab / AF647 (labelled) / #007 / Sino Biological / 40150-R007 / MA14FE2702 / 1:100 [Immunofluorescence]
B38 monoclonal antibody, SARS-CoV-2 receptor binding domain; produced at Pfizer for internal research (no catalogue number); 10 µg/mL (biolayer inferometry)
VSV-G Antibody (clone 8G5F11) / purified / monoclonal / Kerafast Inc. / EB0010 / - / 1:2000

Secondary antibodies and others:
Peroxidase AffiniPure Goat Anti-Mouse IgG, Fcγ fragment specific / HRP / polyclonal / Jackson ImmunoResearch / 115-035-071 / 144460 / 1:15000 [S1- and RBD-specific serum Ab, mouse]
Anti-Rabbit IgG (whole molecule)–Peroxidase antibody produced in goat / HRP / polyclonal / Sigma Aldrich / A0545 / 028M4755V / 1:10000 [Western blot]
AffiniPure Goat Anti-Rabbit IgG (H+L) / AF488 / polyclonal / Jackson ImmunoResearch / 111-545-003 / 122290 / 1:300 [Immunofluorescence]
AffiniPure Goat Anti-Mouse IgG, Fcγ fragment specific (min X Hu, Bov, Hrs Sr Prot) / HRP / polyclonal / Jackson ImmunoResearch / 115-005-071 / 107421 / 1:56.7 [SPR spectroscopy of polyclonal mouse immune sera]
goat anti-human polyclonal secondary antibody / R-PE / polyclonal / Jackson ImmunoResearch / 109-115-098 / 147186 / 1:500
Mouse IgG-UNLB / Purified / polyclonal / Southern Biotech / 0107-01 / D2519-N640 / 1:300 - 1:656100 [S1- and RBD-specific serum Ab, mouse]
Fixable Viability Dye / eF780 / - / eBioscience / 65-0865-14 / 2178170 / 1:1000 and 1:1600 (mouse flow cytometry)
Fixable Viability Dye / eF450 / - / eBioscience / 65-0863-14 / 2143488 / 1:500 (HEK293T/17 flow cytometry)
Fixable Viability Dye / eF780 / - / eBioscience / 65-0865-14 / 2186489 / 1:5000 (rhesus flow cytometry)
Streptavidin / BV421 / - / BD Bioscience / 563259 / 9197684 / 1:200 [mouse flow cytometry]
Concanavalin A / AF594 / - / ThermoFisher Scientific / C11253 / 2160047 / 1:100 [Immunofluorescence]
Lectin GS-II From Griffonia simplicifolia / AF594 / - / ThermoFisher Scientific / L21416 / 2047156 / 1:100 [Immunofluorescence]
Hoechst 33342 / - / - / ThermoFisher Scientific / H3570 / 1733139 / 1:5000 [Immunofluorescence]

Validation

Commercial available Western blot, flow cytometry and immunofluorescence antibodies were selected based on their antigen

Validation	specificity and suggested application as described on the manufacturer`s website and data sheets. Secondary antibodies and others were validated by the manufacturers for the different detection methods. All antibody concentrations for staining were optimized by titrating down each reagent starting at the manufacturer`s recommendation. The optimal amounts of the reagents were defined by (i) minimal unspecific shift of the negative population (flow cytometry) and (ii) a maximal separation of the negative and positive population (flow cytometry) or (iii) no minimal to no background signal (ELISA, western Blot, immunofluorescence, SPR). The specificity of the B38 monoclonal antibody was originally described in Wu et al., Science 368:1274-8. The specificity was confirmed in these experiments by the absence of a background signal by biolayer inferometry and presence of signal when reacted with SARS-CoV-2 spike antigens with identities confirmed by structure determination.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Human embryonic kidney (HEK)293T/17, Cercopithecus aethiops kidney Vero 76 and CCL81 cells (all ATCC); human embryonic kidney Expi293F™ (Thermo Fisher Scientific)
Authentication	Reauthentication of cell lines was performed by short tandem repeat (STR) profiling at supplier
Mycoplasma contamination	All used cell lines tested negative for mycoplasma contamination
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	Male rhesus macaques (Macaca mulatta) (2–4 years) Female BALB/c mice (Janvier; 8-12 weeks)
Wild animals	The study did not involve wild animals.
Field-collected samples	The study did not involve animals collected from the field.
Ethics oversight	All mouse studies were performed at BioNTech SE, and protocols were approved by the local authorities (local welfare committee), conducted according to Federation of European Laboratory Animal Science Associations recommendations and in compliance with the German Animal Welfare Act and Directive 2010/63/EU. Only animals with an unobjectionable health status were selected for testing procedures. Immunisations for the non-human primate (NHP) study were performed at the University of Louisiana at Lafayette-New Iberia Research Centre (NIRC), which is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC, Animal Assurance #: 000452). The work was in accordance with USDA Animal Welfare Act and Regulations and the NIH Guidelines for Research Involving Recombinant DNA Molecules, and Biosafety in Microbiological and Biomedical Laboratories. All procedures performed on these animals were in accordance with regulations and established guidelines and were reviewed and approved by an Institutional Animal Care and Use Committee or through an ethical review process. Infectious SARS-CoV-2 challenge of NHPs following immunisation was performed at the Southwest National Primate Research Centre (SNPRC), Texas Biomedical Research Institute, which is also accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC, Animal Assurance #: 000246). Animal husbandry followed standards recommended by AAALAC International and the NIH Guide for the Care of Use of Laboratory Animals. This study was approved by the Texas Biomedical Research Institute Animal Care and Use Committee.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Human research participants

Policy information about studies involving human research participants

Population characteristics	This manuscript describes preclinical studies. As a benchmark for the non-human primate serology, SARS-CoV-2 neutralising titers and RBD-binding IgG levels of a panel of human SARS-CoV-2/COVID-19 convalescent sera are reproduced, verbatim, from three clinical publications (Sahin et al., Nature 10.1038/s41586-020-2814-7, 2020; Mulligan et al., Nature 10.1038/s41586-020-2639-4, 2020; Walsh et al., The New England Journal of Medicine; 10.1056/NEJMoa2027906, 2020). Please refer to the clinical reports for background to the referenced clinical data.
Recruitment	This manuscript describes preclinical studies. See the clinical reports for background to the referenced clinical data.
Ethics oversight	This manuscript describes preclinical studies. See the clinical reports for background to the referenced clinical data.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	This manuscript describes preclinical studies. See the clinical reports for background to the referenced clinical data.
Study protocol	This manuscript describes preclinical studies. See the clinical reports for background to the referenced clinical data.
Data collection	This manuscript describes preclinical studies. See the clinical reports for background to the referenced clinical data.
Outcomes	This manuscript describes preclinical studies. See the clinical reports for background to the referenced clinical data.

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	Mice: For flow cytometry or ELISpot, blood or cell suspensions from lymph node and spleen were used directly or after peptide stimulation. Peripheral blood was collected from the retro-orbital venous plexus or vena facialis under isoflurane anaesthesia. Spleen single-cell suspensions were prepared in PBS by mashing tissue against the surface of a 70 µm cell strainer (BD Falcon) using the plunger of a 3-mL syringe (BD Biosciences). Erythrocytes were removed by hypotonic lysis. Popliteal, inguinal and iliac lymph nodes were pooled, cut into pieces, digested with collagenase D (1 mg/mL; Roche) and passed through cell strainers. For intracellular stains, cells were fixed and permeabilized using the eBioscience™ Foxp3/ Transcription Factor Staining Buffer Set. NHP: Blood for serum and PBMCs was collected in compliance with animal protocol 2017-8725-023 approved by the NIRC Institutional Animal Care and Use Committee. Animals were anesthetised with ketamine HCl (10 mg/kg; IM) during blood collection and immunisation, and monitored for adequate sedation.
Instrument	Cell culture cells were acquired on a FACSCanto II flow cytometer (BD Biosciences). Mouse cells were acquired on a BD Symphony A3 or BD Celesta (B-cell subtyping) flow cytometer (BD Bioscience). NHP cells were analyzed on a LSR Fortessa X-20
Software	Cell culture cells were analyzed using BD FACSDiva software version 8.0.1 and analysed by FlowJo software version 10.6.2 (FlowJo LLC, BD Biosciences). Mouse cells were analyzed using BD FACSDiva software version 9.1 or 8.0.1.1, respectively, and analysed with FlowJo 10.6 (FlowJo LLC, BD Biosciences). NHP cells were analyzed using FlowJo (10.4.1).
Cell population abundance	Sorted CD4 CD8 T cells from mouse were confimed following magnetic bead separation.
Gating strategy	The gating strategies are detailed in the supplementary information. Mouse: Flow cytometry gating strategy for the identification of IFNγ, IL-2, and TNF secreting CD8+ T cells in the mouse spleen. was performed after CD8+ T cells were gated within single, viable lymphocytes, excluding CD4+ T cells. Flow cytometry gating strategy for identification of TFH cells, activated T cells and B cells in lymph nodes and the spleen was performed by CD3+CD19- T cells gating within single, viable lymphocytes. CD4+ and CD8+ T cells were gated from CD3+ cells; TFH cells were gated from CD4+ T cells and defined as CD4+ T-bet- GATA3- CD44+ CD62L- PD-1+ CXCR5+ cells. Flow cytometry gating strategy for the identification of B cells in lymph nodes and the spleen was done by gating activated B cells within single, viable lymphocytes defined as IgD-Dump (CD4, CD8, F4/80, GR-1)- cells. Plasma cells (PC) were gated from activated B cells and defined as CD138+ B220low/- cells. Switched B cells were gated from non-PC and defined as CD19+ CD138- IgM-. Germinal centre (GC) and IgG1+ and IgG2a+ B cells were gated from switched B cells and defined as CD19+ IgM- CD38- CD95+ and CD19+ IgM- IgG1+/IgG2a+, respectively. Flow cytometry gating strategy for the identification of T cells, B cells and TFH cells in peripheral blood was performed by gating CD3+ CD19- T cells within single, viable lymphocytes. CD4+ and CD8+ T cells were gated from CD3+ CD19- cells. TFH cells were gated from CD4+ T cells and defined as CD4+ T-bet- GATA3- CD44+ CD62L- PD-1+ CXCR5+ cells. Rhesus macaque: Flow cytometry gating strategy for identification of spike-specific SARS-CoV-2 modRNA vaccine BNT162b2-induced T cells started with events acquired with a constant flow stream and fluorescence intensity, viable cells, lymphocytes and single events were identified and gated. Within singlet lymphocytes, CD20- CD3+ T cells were identified and gated into CD4+ T cells and CD8+ T cells. Antigen-specific CD4+ T cells were identified by gating on CD154 and cytokine-positive cells, and CD8+ T cells were identified by gating on CD69 and cytokine-positive cells. The antigen-specific cells were used for further analysis. in vitro:

Flow cytometry gating strategy for the identification of HEK293T cells transfected with BNT162b1 or BNT162b2, or BNT162b1-RNA or BNT162b2-RNA using a transfection reagent or no RNA (control) was performed by gating S1+ HEK293T cells within single, viable HEK293T cells.

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

EXHIBIT 9

VACCINE INFORMATION FACT SHEET FOR RECIPIENTS AND CAREGIVERS ABOUT COMIRNATY (COVID-19 VACCINE, mRNA) AND THE PFIZER-BIONTECH COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19) FOR USE IN INDIVIDUALS 12 YEARS OF AGE AND OLDER

FOR 12 YEARS OF AGE AND OLDER

You are being offered either COMIRNATY (COVID-19 Vaccine, mRNA) or the Pfizer-BioNTech COVID-19 Vaccine to prevent Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2.

This Vaccine Information Fact Sheet for Recipients and Caregivers comprises the Fact Sheet for the authorized Pfizer-BioNTech COVID-19 Vaccine and also includes information about the U.S. Food and Drug Administration (FDA)-licensed vaccine, COMIRNATY (COVID-19 Vaccine, mRNA) for use in individuals 12 years of age and older[1].

The FDA-approved COMIRNATY (COVID-19 Vaccine, mRNA) and the Pfizer-BioNTech COVID-19 Vaccine authorized under Emergency Use Authorization (EUA) for individuals 12 years of age and older, when prepared according to their respective instructions for use, can be used interchangeably.[2]

COMIRNATY (COVID-19 Vaccine, mRNA) is an FDA-approved COVID-19 vaccine made by Pfizer for BioNTech. It is approved as a 2-dose series for prevention of COVID-19 in individuals 12 years of age and older. It is also authorized under EUA to provide:

- **a third primary series dose to individuals 12 years of age and older with certain kinds of immunocompromise;**
- **a first booster dose to individuals 12 years of age and older who have completed a primary series with Pfizer-BioNTech COVID-19 Vaccine or COMIRNATY (COVID-19 Vaccine, mRNA);**
- **a first booster dose to individuals 18 years of age and older who have completed primary vaccination with another authorized or approved**

[1] You may receive this Vaccine Information Fact Sheet even if your child is 11 years old. Children who will turn from 11 years to 12 years of age between doses in the primary regimen may receive, for any dose in the primary regimen, either: (1) the Pfizer-BioNTech COVID-19 Vaccine authorized for use in individuals 5 through 11 years of age; or (2) COMIRNATY (COVID-19 Vaccine, mRNA) or the Pfizer-BioNTech COVID-19 Vaccine authorized for use in individuals 12 years of age and older.

[2] When prepared according to their respective instructions for use, the FDA-approved COMIRNATY (COVID-19 Vaccine, mRNA) and the EUA-authorized Pfizer-BioNTech COVID-19 Vaccine for individuals 12 years of age and older can be used interchangeably without presenting any safety or effectiveness concerns.

COVID-19 vaccine. The booster schedule is based on the labeling information of the vaccine used for the primary series;
- **a second booster dose to individuals 50 years of age and older who have received a first booster dose of any authorized or approved COVID-19 vaccine; and**
- **a second booster dose to individuals 12 years of age and older with certain kinds of immunocompromise and who have received a first booster dose of any authorized or approved COVID-19 vaccine.**

The Pfizer-BioNTech COVID-19 Vaccine has received EUA from FDA to provide:
- **a 2-dose primary series to individuals 12 years of age and older;**
- **a third primary series dose to individuals 12 years of age and older with certain kinds of immunocompromise;**
- **a first booster dose to individuals 12 years of age and older who have completed a primary series with Pfizer-BioNTech COVID-19 Vaccine or COMIRNATY (COVID-19 Vaccine, mRNA);**
- **a first booster dose to individuals 18 years of age and older who have completed primary vaccination with another authorized or approved COVID-19 vaccine. The booster schedule is based on the labeling information of the vaccine used for the primary series;**
- **a second booster dose to individuals 50 years of age and older who have received a first booster dose of any authorized or approved COVID-19 vaccine; and**
- **a second booster dose to individuals 12 years of age and older with certain kinds of immunocompromise and who have received a first booster dose of any authorized or approved COVID-19 vaccine.**

This Vaccine Information Fact Sheet contains information to help you understand the risks and benefits of COMIRNATY (COVID-19 Vaccine, mRNA) and the Pfizer-BioNTech COVID-19 Vaccine, which you may receive because there is currently a pandemic of COVID-19. Talk to your vaccination provider if you have questions.

This Fact Sheet may have been updated. For the most recent Fact Sheet, please see www.cvdvaccine.com.

WHAT YOU NEED TO KNOW BEFORE YOU GET THIS VACCINE

WHAT IS COVID-19?

COVID-19 disease is caused by a coronavirus called SARS-CoV-2. You can get COVID-19 through contact with another person who has the virus. It is predominantly a respiratory illness that can affect other organs. People with COVID-19 have had a wide range of symptoms reported, ranging from mild symptoms to severe illness leading to death. Symptoms may appear 2 to 14 days after exposure to the virus. Symptoms may include: fever or chills; cough; shortness of breath; fatigue; muscle or body aches;

headache; new loss of taste or smell; sore throat; congestion or runny nose; nausea or vomiting; diarrhea.

WHAT IS COMIRNATY (COVID-19 VACCINE, mRNA) AND HOW IS IT RELATED TO THE PFIZER-BIONTECH COVID-19 VACCINE?

COMIRNATY (COVID-19 Vaccine, mRNA) and the Pfizer-BioNTech COVID-19 Vaccine, when prepared according to their respective instructions for use, can be used interchangeably.

For more information on EUA, see the "**What is an Emergency Use Authorization (EUA)?**" section at the end of this Fact Sheet.

WHAT SHOULD YOU MENTION TO YOUR VACCINATION PROVIDER BEFORE YOU GET THE VACCINE?
Tell the vaccination provider about all of your medical conditions, including if you:

- have any allergies
- have had myocarditis (inflammation of the heart muscle) or pericarditis (inflammation of the lining outside the heart)
- have a fever
- have a bleeding disorder or are on a blood thinner
- are immunocompromised or are on a medicine that affects your immune system
- are pregnant or plan to become pregnant
- are breastfeeding
- have received another COVID-19 vaccine
- have ever fainted in association with an injection

HOW IS THE VACCINE GIVEN?
The Pfizer-BioNTech COVID-19 Vaccine or COMIRNATY (COVID-19 Vaccine, mRNA) will be given to you as an injection into the muscle.

Primary Series: The vaccine is administered as a 2-dose series, 3 weeks apart. A third primary series dose may be administered at least 4 weeks after the second dose to individuals with certain kinds of immunocompromise.

Booster Dose:

- A first booster dose of the vaccine may be administered at least 5 months after completion of a primary series of the Pfizer-BioNTech COVID-19 Vaccine or COMIRNATY (COVID-19 Vaccine, mRNA) to individuals 12 years of age and older.

- A first booster dose of the vaccine may be administered to individuals 18 years of age and older who have completed primary vaccination with another authorized or approved COVID-19 vaccine. Please check with your healthcare provider regarding timing of the booster dose.
- A second booster dose of the vaccine may be administered to individuals 50 years of age and older at least 4 months after receipt of a first booster dose of any authorized or approved COVID-19 vaccine.
- A second booster dose of the vaccine may be administered at least 4 months after receipt of a first booster dose of any authorized or approved COVID-19 vaccine to individuals 12 years of age and older with certain kinds of immunocompromise.

The vaccine may not protect everyone.

WHO SHOULD NOT GET THE VACCINE?
You should not get the vaccine if you:

- had a severe allergic reaction after a previous dose of this vaccine
- had a severe allergic reaction to any ingredient of this vaccine.

WHAT ARE THE INGREDIENTS IN THE VACCINES?
COMIRNATY (COVID-19 Vaccine, mRNA) and the authorized formulations of the vaccine include the following ingredients:

- mRNA and lipids (((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-Distearoyl-sn-glycero-3-phosphocholine, and cholesterol).

Pfizer-BioNTech COVID-19 vaccines for individuals 12 years of age and older contain 1 of the following sets of additional ingredients; ask the vaccination provider which version is being administered:

- potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose

OR

- tromethamine, tromethamine hydrochloride, and sucrose

COMIRNATY (COVID-19 Vaccine, mRNA) contains 1 of the following sets of additional ingredients; ask the vaccination provider which version is being administered:

- potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose

OR

- tromethamine, tromethamine hydrochloride, and sucrose

HAS THE VACCINE BEEN USED BEFORE?
Yes. In clinical trials, approximately 23,000 individuals 12 years of age and older have received at least 1 dose of the vaccine. Data from these clinical trials supported the Emergency Use Authorization of the Pfizer-BioNTech COVID-19 Vaccines and the approval of COMIRNATY (COVID-19 Vaccine, mRNA). Millions of individuals have received the vaccine under EUA since December 11, 2020. The vaccine that is

authorized for use in individuals 12 years of age and older includes two formulations; one that was studied in clinical trials and used under EUA, and one with the same mRNA and lipids but different inactive ingredients. The use of the different inactive ingredients helps stabilize the vaccine under refrigerated temperatures and the formulation can be administered without dilution.

WHAT ARE THE BENEFITS OF THE VACCINE?
The vaccine has been shown to prevent COVID-19.

The duration of protection against COVID-19 is currently unknown.

WHAT ARE THE RISKS OF THE VACCINE?
There is a remote chance that the vaccine could cause a severe allergic reaction. A severe allergic reaction would usually occur within a few minutes to 1 hour after getting a dose of the vaccine. For this reason, your vaccination provider may ask you to stay at the place where you received your vaccine for monitoring after vaccination. Signs of a severe allergic reaction can include:

- Difficulty breathing
- Swelling of your face and throat
- A fast heartbeat
- A bad rash all over your body
- Dizziness and weakness

Myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) have occurred in some people who have received the vaccine, more commonly in adolescent males and adult males under 40 years of age than among females and older males. In most of these people, symptoms began within a few days following receipt of the second dose of vaccine. The chance of having this occur is very low. You should seek medical attention right away if you have any of the following symptoms after receiving the vaccine:

- Chest pain
- Shortness of breath
- Feelings of having a fast-beating, fluttering, or pounding heart

Side effects that have been reported with the vaccine include:

- Severe allergic reactions
- Non-severe allergic reactions such as rash, itching, hives, or swelling of the face
- Myocarditis (inflammation of the heart muscle)
- Pericarditis (inflammation of the lining outside the heart)
- Injection site pain
- Tiredness
- Headache
- Muscle pain

- Chills
- Joint pain
- Fever
- Injection site swelling
- Injection site redness
- Nausea
- Feeling unwell
- Swollen lymph nodes (lymphadenopathy)
- Decreased appetite
- Diarrhea
- Vomiting
- Arm pain
- Fainting in association with injection of the vaccine

These may not be all the possible side effects of the vaccine. Serious and unexpected side effects may occur. The possible side effects of the vaccine are still being studied in clinical trials.

WHAT SHOULD I DO ABOUT SIDE EFFECTS?
If you experience a severe allergic reaction, call 9-1-1, or go to the nearest hospital.

Call the vaccination provider or your healthcare provider if you have any side effects that bother you or do not go away.

Report vaccine side effects to FDA/CDC Vaccine Adverse Event Reporting System (VAERS). The VAERS toll-free number is 1-800-822-7967 or report online to https://vaers.hhs.gov/reportevent.html. Please include either "COMIRNATY (COVID-19 Vaccine, mRNA)" or "Pfizer-BioNTech COVID-19 Vaccine EUA", as appropriate, in the first line of box #18 of the report form.

In addition, you can report side effects to Pfizer Inc. at the contact information provided below.

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

You may also be given an option to enroll in v-safe. V-safe is a voluntary smartphone-based tool that uses text messaging and web surveys to check in with people who have been vaccinated to identify potential side effects after COVID-19 vaccination. V-safe asks questions that help CDC monitor the safety of COVID-19 vaccines. V-safe also provides second-dose reminders if needed and live telephone follow-up by CDC if participants report a significant health impact following COVID-19 vaccination. For more information on how to sign up, visit: www.cdc.gov/vsafe.

WHAT IF I DECIDE NOT TO GET COMIRNATY (COVID-19 VACCINE, mRNA) OR THE PFIZER-BIONTECH COVID-19 VACCINE?
Under the EUA, it is your choice to receive or not receive the vaccine. Should you decide not to receive it, it will not change your standard medical care.

ARE OTHER CHOICES AVAILABLE FOR PREVENTING COVID-19 BESIDES COMIRNATY (COVID-19 VACCINE, mRNA) OR THE PFIZER-BIONTECH COVID-19 VACCINE?
Another choice for preventing COVID-19 is SPIKEVAX, an FDA-approved COVID-19 vaccine. Other vaccines to prevent COVID-19 may be available under Emergency Use Authorization.

CAN I RECEIVE THE COMIRNATY (COVID-19 VACCINE, mRNA) OR PFIZER-BIONTECH COVID-19 VACCINE AT THE SAME TIME AS OTHER VACCINES?
Data have not yet been submitted to FDA on administration of COMIRNATY (COVID-19 Vaccine, mRNA) or the Pfizer-BioNTech COVID-19 Vaccine at the same time with other vaccines. If you are considering receiving COMIRNATY (COVID-19 Vaccine, mRNA) or the Pfizer-BioNTech COVID-19 Vaccine with other vaccines, discuss your options with your healthcare provider.

WHAT IF I AM IMMUNOCOMPROMISED?
If you are immunocompromised, you may receive a third primary series dose of the vaccine. The third dose may still not provide full immunity to COVID-19 in people who are immunocompromised, and you should continue to maintain physical precautions to help prevent COVID-19. In addition, after you received a first booster dose, you may receive a second booster dose of the vaccine if you are 12 years of age or older. Your close contacts should be vaccinated as appropriate.

WHAT IF I AM PREGNANT OR BREASTFEEDING?
If you are pregnant or breastfeeding, discuss your options with your healthcare provider.

WILL THE VACCINE GIVE ME COVID-19?
No. The vaccine does not contain SARS-CoV-2 and cannot give you COVID-19.

KEEP YOUR VACCINATION CARD
When you get your first dose, you will get a vaccination card to show you when to return for your next dose(s) of the vaccine. Remember to bring your card when you return.

ADDITIONAL INFORMATION
If you have questions, visit the website or call the telephone number provided below.

To access the most recent Fact Sheets, please scan the QR code provided below.

Global website	Telephone number
www.cvdvaccine.com	1-877-829-2619 (1-877-VAX-CO19)

HOW CAN I LEARN MORE?
- Ask the vaccination provider.
- Visit CDC at https://www.cdc.gov/coronavirus/2019-ncov/index.html.
- Visit FDA at https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.
- Contact your local or state public health department.

WHERE WILL MY VACCINATION INFORMATION BE RECORDED?
The vaccination provider may include your vaccination information in your state/local jurisdiction's Immunization Information System (IIS) or other designated system. This will ensure that you receive the same vaccine when you return for the second dose. For more information about IISs visit: https://www.cdc.gov/vaccines/programs/iis/about.html.

CAN I BE CHARGED AN ADMINISTRATION FEE FOR RECEIPT OF THE COVID-19 VACCINE?
No. At this time, the provider cannot charge you for a vaccine dose and you cannot be charged an out-of-pocket vaccine administration fee or any other fee if only receiving a COVID-19 vaccination. However, vaccination providers may seek appropriate reimbursement from a program or plan that covers COVID-19 vaccine administration fees for the vaccine recipient (private insurance, Medicare, Medicaid, Health Resources & Services Administration [HRSA] COVID-19 Uninsured Program for non-insured recipients).

WHERE CAN I REPORT CASES OF SUSPECTED FRAUD?
Individuals becoming aware of any potential violations of the CDC COVID-19 Vaccination Program requirements are encouraged to report them to the Office of the Inspector General, U.S. Department of Health and Human Services, at 1-800-HHS-TIPS or https://TIPS.HHS.GOV.

WHAT IS THE COUNTERMEASURES INJURY COMPENSATION PROGRAM?
The Countermeasures Injury Compensation Program (CICP) is a federal program that may help pay for costs of medical care and other specific expenses of certain people who have been seriously injured by certain medicines or vaccines, including this

vaccine. Generally, a claim must be submitted to the CICP within one (1) year from the date of receiving the vaccine. To learn more about this program, visit www.hrsa.gov/cicp/ or call 1-855-266-2427.

WHAT IS AN EMERGENCY USE AUTHORIZATION (EUA)?
An EUA is a mechanism to facilitate the availability and use of medical products, including vaccines, during public health emergencies, such as the current COVID-19 pandemic. An EUA is supported by a Secretary of Health and Human Services (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological products during the COVID-19 pandemic. A product authorized for emergency use has not undergone the same type of review by FDA as an FDA-approved product.

FDA may issue an EUA when certain criteria are met, which includes that there are no adequate, approved, and available alternatives. In addition, the FDA decision is based on the totality of the scientific evidence available showing that the product may be effective to prevent COVID-19 during the COVID-19 pandemic and that the known and potential benefits of the product outweigh the known and potential risks of the product. All of these criteria must be met to allow for the product to be used during the COVID-19 pandemic.

An EUA is in effect for the duration of the COVID-19 EUA declaration justifying emergency use of this product, unless terminated or revoked (after which the product may no longer be used).

BIONTECH
Manufactured for
BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

Pfizer
Manufactured by
Pfizer Inc., New York, NY 10017

LAB-1451-19.2a

Revised: 8 July 2022

Scan to capture that this Fact Sheet was provided to vaccine recipient for the electronic medical records/immunization information systems.

GDTI: 0886983000332

JS 44 (Rev. 10/20)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. *(SEE INSTRUCTIONS ON NEXT PAGE OF THIS FORM.)*

I. (a) PLAINTIFFS

MODERNATX, INC. and MODERNA US, INC.

(b) County of Residence of First Listed Plaintiff Middlesex County
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorneys *(Firm Name, Address, and Telephone Number)*

Wilmer Cutler Pickering Hale and Dorr, 60 State Street, Boston, MA 02109, (617) 526-6000

DEFENDANTS

PFIZER INC., BIONTECH SE, BIONTECH MANUFACTURING GMBH, and BIONTECH US INC.

County of Residence of First Listed Defendant New York County
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

Attorneys *(If Known)*

II. BASIS OF JURISDICTION *(Place an "X" in One Box Only)*

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question *(U.S. Government Not a Party)*
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity *(Indicate Citizenship of Parties in Item III)*

III. CITIZENSHIP OF PRINCIPAL PARTIES *(Place an "X" in One Box for Plaintiff and One Box for Defendant)*

(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT *(Place an "X" in One Box Only)*

Click here for: Nature of Suit Code Descriptions.

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excludes Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
- ☐ 196 Franchise

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury
- ☐ 362 Personal Injury - Medical Malpractice

PERSONAL INJURY
- ☐ 365 Personal Injury - Product Liability
- ☐ 367 Health Care/ Pharmaceutical Personal Injury Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

FORFEITURE/PENALTY
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Management Relations
- ☐ 740 Railway Labor Act
- ☐ 751 Family and Medical Leave Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Employee Retirement Income Security Act

IMMIGRATION
- ☐ 462 Naturalization Application
- ☐ 465 Other Immigration Actions

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 835 Patent - Abbreviated New Drug Application
- ☐ 840 Trademark
- ☐ 880 Defend Trade Secrets Act of 2016

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ☐ 375 False Claims Act
- ☐ 376 Qui Tam (31 USC 3729(a))
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 480 Consumer Credit (15 USC 1681 or 1692)
- ☐ 485 Telephone Consumer Protection Act
- ☐ 490 Cable/Sat TV
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 893 Environmental Matters
- ☐ 895 Freedom of Information Act
- ☐ 896 Arbitration
- ☐ 899 Administrative Procedure Act/Review or Appeal of Agency Decision
- ☐ 950 Constitutionality of State Statutes

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

CIVIL RIGHTS
- ☐ 440 Other Civil Rights
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 445 Amer. w/Disabilities - Employment
- ☐ 446 Amer. w/Disabilities - Other
- ☐ 448 Education

PRISONER PETITIONS

Habeas Corpus:
- ☐ 463 Alien Detainee
- ☐ 510 Motions to Vacate Sentence
- ☐ 530 General
- ☐ 535 Death Penalty

Other:
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition
- ☐ 560 Civil Detainee - Conditions of Confinement

V. ORIGIN *(Place an "X" in One Box Only)*

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from Another District *(specify)* ☐ 6 Multidistrict Litigation - Transfer ☐ 8 Multidistrict Litigation - Direct File

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing ***(Do not cite jurisdictional statutes unless diversity)***:
35 U.S.C. § 271

Brief description of cause:
Patent infringement

VII. REQUESTED IN COMPLAINT:

☐ CHECK IF THIS IS A **CLASS ACTION** UNDER RULE 23, F.R.Cv.P.

DEMAND $

CHECK YES only if demanded in complaint:

JURY DEMAND: ☒ Yes ☐ No

VIII. RELATED CASE(S) IF ANY

(See instructions): JUDGE _____ DOCKET NUMBER _____

DATE 08/26/2022

SIGNATURE OF ATTORNEY OF RECORD /s/ William F. Lee

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

1. **Title of case (name of first party on each side only)** ModernaTX, Inc. v. Pfizer Inc.

2. **Category in which the case belongs based upon the numbered nature of suit code listed on the civil cover sheet. (See local rule 40.1(a)(1)).**

☑ **I.** **160, 400, 410, 441, 535, 830*, 835*, 850, 880, 891, 893, R.23, REGARDLESS OF NATURE OF SUIT.**

☐ **II.** **110, 130, 190, 196, 370, 375, 376, 440, 442, 443, 445, 446, 448, 470, 751, 820*, 840*, 895, 896, 899.**

☐ **III.** **120, 140, 150, 151, 152, 153, 195, 210, 220, 230, 240, 245, 290, 310, 315, 320, 330, 340, 345, 350, 355, 360, 362, 365, 367, 368, 371, 380, 385, 422, 423, 430, 450, 460, 462, 463, 465, 480, 485, 490, 510, 530, 540, 550, 555, 560, 625, 690, 710, 720, 740, 790, 791, 861-865, 870, 871, 890, 950.**

***Also complete AO 120 or AO 121. for patent, trademark or copyright cases.**

3. **Title and number, if any, of related cases. (See local rule 40.1(g)). If more than one prior related case has been filed in this district please indicate the title and number of the first filed case in this court.**

4. **Has a prior action between the same parties and based on the same claim ever been filed in this court?**

YES ☐ **NO** ☑

5. **Does the complaint in this case question the constitutionality of an act of congress affecting the public interest? (See 28 USC §2403)**

YES ☐ **NO** ☑

If so, is the U.S.A. or an officer, agent or employee of the U.S. a party?

YES ☐ **NO** ☐

6. **Is this case required to be heard and determined by a district court of three judges pursuant to title 28 USC §2284?**

YES ☐ **NO** ☑

7. **Do all of the parties in this action, excluding governmental agencies of the United States and the Commonwealth of Massachusetts ("governmental agencies"), residing in Massachusetts reside in the same division? - (See Local Rule 40.1(d)).**

YES ☑ **NO** ☐

A. **If yes, in which division do all of the non-governmental parties reside?**

Eastern Division ☑ **Central Division** ☐ **Western Division** ☐

B. **If no, in which division do the majority of the plaintiffs or the only parties, excluding governmental agencies, residing in Massachusetts reside?**

Eastern Division ☐ **Central Division** ☐ **Western Division** ☐

8. **If filing a Notice of Removal - are there any motions pending in the state court requiring the attention of this Court? (If yes, submit a separate sheet identifying the motions)**

YES ☐ **NO** ☐

(PLEASE TYPE OR PRINT)

ATTORNEY'S NAME William F. Lee

ADDRESS Wilmer Cutler Pickering Hale and Dorr, 60 State Street, Boston, MA 02109

TELEPHONE NO. (617) 526-6000